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ABSTRACT

Important new medical findings and advances in heart, lung, and blood research with goals of encouraging practical applications are presented in this supplement to the 12th report of the National Heart, Lung, and Blood Advisory Council. The findings are the result of a 10-year research program directed to the highest identified priorities in preventing and controlling heart, blood vessel, lung, and blood diseases. The collection of articles present the implications of recent advances for individuals and public health. These articles include: (1) from theory to practice--the biomedical research spectrum; (2) pathways to discovery (providing examples of serendipitous scientific breakthroughs); (3) function and failure--visualizing heart, lung, and blood disease; (4) era of technology (reviewing major advances in diagnostic techniques); (5) lifesavers--advances in medical treatment; (6) CPR--reviving the heart after cardiac arrest; (7) improving the outlook for children (8) health education/risk reduction--helping healthy children stay healthy; (9) prevention--Farmingham's legacy; (10) judging the news (offering guidelines for assessing media's portrayal of scientific breakthroughs); (11) looking ahead--heart, lung, and blood medicine in the year 2000; (12) research--how is it supported?; and (13) heart, lung, and blood disease--health and economic consequences. (ML)

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Momentum Toward Health

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National Heart, Lung, and Blood Advisory Council

Catherine B. Bauer
St. Mary's, Pennsylvania

Richard Carleton, M.D.
Pawtucket, Rhode Island

John E. Connolly, M.D.
Irvine, California

Eliot Corday, M.D.
Los Angeles, California

Dale H. Cowan, M.D., J.D.
Cleveland, Ohio

Suzanne P. Cummings
Beverly Hills, California

Michael E. DeBakey, M.D., LL.D.
Houston, Texas

Matthew B. Divertie, M.D.
Rochester, Minnesota

Celia J. Finn, M.D.
St. Louis, Missouri

Carl Franzblau, Ph.D.
Boston, Massachusetts

Roberta M. Goldring, M.D.
New York, New York

C. Charles Jackson, Jr.
Minneapolis, Minnesota

Charles D. Knight, Jr., M.D.
Rochester, Minnesota

Sanford A. Mullen, M.D.
Jacksonville, Florida

Harold R. Roberts, M.D.
Chapel Hill, North Carolina

John Ross, Jr., M.D.
La Jolla, California

Joseph C. Ross, M.D.
Nashville, Tennessee

Jane S. Scott
Graham, North Carolina

Claude Lenfant, M.D. (Chairman)
Director
National Heart, Lung, and Blood Institute

Ex Officio

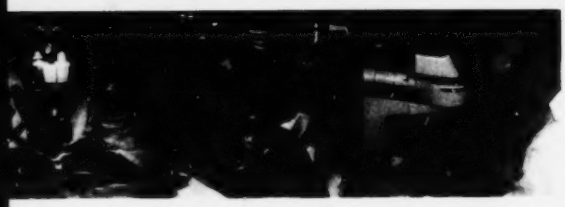
William P. Baker, M.D., Ph.D.,
Bethesda, Maryland

Ross D. Fletcher, M.D.
Washington, D.C.

Bernadine Healy, M.D.
Washington, D.C.

James B. Wyngaarden, M.D.
Director
National Institutes of Health

Margaret M. Heckler
Secretary
Department of Health and Human Services



Contents

Foreword 5

From Theory to Practice
The Biomedical Research Spectrum 7

Pathways to Discovery 17

Function and Failure
Visualizing Heart, Lung, and Blood Disease 31

The Era of Technology 39

Lifesavers
Advances in Medical Treatment 47

CPR
Reviving the Heart After Cardiac Arrest 54

Improving the Outlook for Children 57

Health Education/ Risk Reduction
Helping Healthy Children Stay Healthy 62

Prevention
Framingham's Legacy 65

Judging the News 72

Looking Ahead
Heart, Lung, and Blood Medicine in the Year 2000 73

Research
How Is It Supported? 84

Heart, Lung, and Blood Disease
Health and Economic Consequences 84

Momentum Toward Health
The Research Dynamic

As a research organization of the Federal Government, the National Heart, Lung, and Blood Institute (NHLBI) has a mandate to stimulate and produce new knowledge. To ensure that research advances are put to wide scientific and practical use, the Institute also is charged with disseminating the new information that its studies generate.

This publication presents important new medical findings and advances in heart, lung, and blood research, with a goal of encouraging their practical application. The articles are directed to a variety of audiences that make use of health information. These include government and private sector decisionmakers, who can bring the new information to bear on planning and policymaking; health professionals, who may want to adopt new concepts in their practices or pass ideas on to their patients; and consumers, who can use research results to live healthier lives.

This publication is a public education supplement to the 12th Report of the National Heart, Lung, and Blood Advisory Council, a group of leading physicians, scientists, and lay persons who have a special interest in heart, lung, and blood medicine and research. The findings discussed are the result of an aggressive 10-year research program directed to the highest identified priorities in preventing and controlling heart, blood vessel, lung, and blood diseases.

The articles that follow present the implications of these advances for individual and public health. Our objective is to provide an understanding of the multistage process of biomedical research, an overview of the progress that has occurred in the past 10 years, and direction in using research results to make healthy lifestyle choices.

The National Heart, Lung, and Blood Advisory Council

The cell separator isolates cells of a specific type for use in basic science experiments or diagnosis of disease.

From Theory to Practice

The Biomedical Research Spectrum

"Science," a philosopher of science once wrote, "is sciencing." It is not a defined collection of formulas but an activity, a way of dealing with experience.

The activity that is biomedical science has many aspects and many actors. Lewis Thomas, in his *Lives of a Cell*, compared the discipline to an immense intellectual beehive. "There is nothing," he said, "to touch the spectacle. In the midst of what seems a collective derangement of minds in total disorder, with bits of information being scattered about, torn to shreds, disintegrated, deconstituted, engulfed, in a kind of activity that seems as random and agitated as that of bees in a disturbed part of the hive, there suddenly emerges, with the purity of a slow phrase of music, a single new piece of truth about nature."

Like the age-old chicken-egg conundrum, we cannot always know which of the activities of science comes first. We need facts to produce new theories, but we also need theories to produce new facts. It is possible, however, to define categories of research activity that occur in the process of turning facts and theories into medical advancements.

As the spectrum below shows, heart, lung, and blood research has at least five stages of activity, from looking for Thomas's new pieces of truth to finding the best ways to put new knowledge into practice. Each one has contributed to the past decade's lifesaving progress in health care.

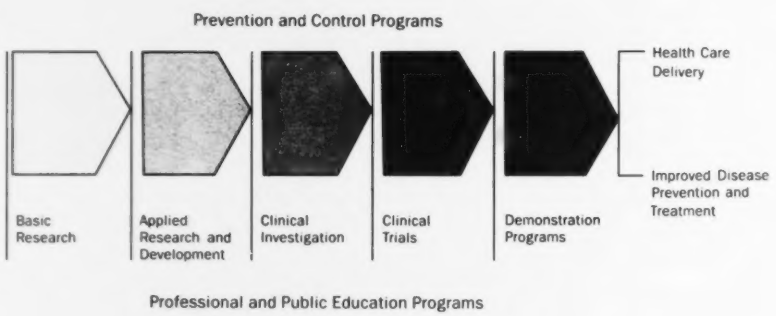
Basic Research

Building Blocks for Discovery

Several decades ago, the prevailing view was that cholesterol quietly inhabited cell membranes and the circulating plasma, largely unnoticed and little understood. Today, from television food advertisements to the cover of *Time* magazine to scientific literature, cholesterol is a household word.

This notorious lipid first came into the spotlight when statistical studies suggested that people with high blood cholesterol levels were more likely to develop heart attacks and strokes. We subsequently learned there is a "good" form of cholesterol (transported by high density lipoprotein or HDL) that seems to protect against these conditions at high concentrations and a "bad" cholesterol (transported by low density lipoprotein or LDL) that is associated with increased risk at high levels. Recent attention has focused on clinical trial results showing that cardiovascular mortality can be reduced by lowering cholesterol levels with drugs.

While these facts and findings have tremendous implications, some issues are even more fundamental. How is cholesterol produced? What causes high cholesterol levels? How do the HDL particles prevent cardiovascular problems? And, most critical of all, what is cholesterol's role in producing the plaque-clogged arteries of atherosclerosis, which ultimately lead to heart attack or stroke?



Basic science has unraveled many of the fundamental characteristics of cholesterol, shown here in a color-enhanced micrograph.

The scientist investigates in the laboratory the basic causes and mechanisms of disease.

These questions are the grist of the basic scientist, who investigates causes and fundamental mechanisms to discover the hows and the whys. Individual steps forward in basic biomedical science, like the thousands of discrete chemical and biological building blocks they unravel, may disclose only a small part of a physiologic or disease process. Taken together, however, these steps lead to the underlying knowledge on which ideas for treatments and cures are based.

What have basic research scientists discovered about cholesterol? First, we know how it is produced and how it is circulated. Certain kinds of fat in the diet are one source of cholesterol, and the one most widely discussed. Cells in the intestines process this dietary cholesterol into esters and release them into the bloodstream. A second source of cholesterol is the liver, which produces it by synthesizing very low density lipoprotein (VLDL) and then converting it into a number of lipoprotein particles, including the risk-associated LDL. LDL contains cholesterol esters and transports them in the blood to various tissues and organs, for example, the adrenal glands, which use cholesterol to make steroid hormones.

Researchers at the University of Texas recently learned that each person's production of cholesterol is controlled by a receptor—a "balancing" device in the plasma membrane of cells. The cholesterol balancing act is two-sided. When normal cells need additional cholesterol to function, they produce additional LDL receptors, which bind circulating LDL particles and release their cholesterol into the cell. When the cell gets enough cholesterol, an enzyme stops production of the new LDL receptors.

The receptors appear to be equally important in preventing overproduction of LDL. The conversion process in the liver that produces LDL from VLDL does not transform all of the VLDL. It leaves behind what is called a remnant particle. The LDL receptors in the liver bind these VLDL remnants and degrade them. Without this binding, the VLDL would remain in the plasma and be converted to additional LDL, producing an unhealthy excess.

This defect, in fact, occurs in the condition known as familial hypercholesterolemia. Basic scientists have found that a genetic defect inhibits production of LDL receptors and causes cholesterol levels among those missing both LDL receptor genes six to eight times above normal. People with the condition almost always develop heart disease, even the larger group that inherits one normal LDL receptor gene.

Work in outlining the metabolic pathways of HDL is currently less well-defined, but studies suggest that HDL may carry cholesterol away from the tissues (where LDL deposits it). Other findings have shown that HDL may prevent cholesterol buildup by blocking the LDL from binding to its receptors in the cells and releasing its cholesterol. Either mechanism would reduce the likelihood that excess cholesterol would accumulate in the arterial linings.

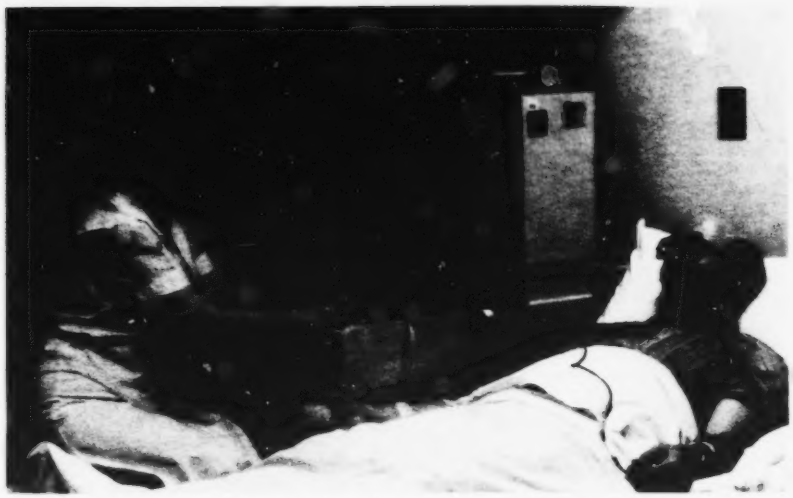
It is this accumulation and the effect it has on platelets, endothelial cells, and the smooth muscle cells in the arterial wall that will be the focus of much basic science research in the coming years. These critical studies will tell us how atherosclerosis and heart disease begin and progress, information that is fundamental to continued improvement in prevention and treatment.

Using New Knowledge to Make New Tools

When Rampal fingers his flute or Segovia his guitar, it may seem prosaic to recall the people who perfected the material for the guitar strings, the technique for fashioning a flute from wood or metal, or the combination of architectural and structural elements that creates concert hall acoustics. Yet these unseen hands are equally responsible for the quality of the music we hear.

Applied researchers make the same kinds of critical, but behind-the-scenes, contributions to medical care. They focus on finding the specific knowledge to take a necessary step in improving care for a particular disease. The results of their studies are the nuts and bolts of medical research: Animal models of a human disease, new diagnostic techniques and devices, and improvements in technologies that meet clinical and economic needs.

A technology for removing selected blood components from whole blood is a good example of applied research and development. In this process, known as apheresis, blood is removed from the body. An automated centrifuge separates substances from the blood, which is then returned to the body. Primitive devices that make basic blood separations have been available most of this century, but a series of technical refinements allowing more sophisticated manipulations have occurred only in the past 10 years. We can now collect 17 medically important elements from donated blood to use for replacement therapy. Platelets, for example, are collected for use in controlling bleeding during coronary bypass surgery. Apheresis also can remove disease-causing substances from the blood and exchange them for electrolyte and other solutions to maintain blood volume.



Apheresis, which separates components from the blood using an automated centrifuge, is a product of applied research and development.

The technique now is being tested clinically for removing circulating autoantibodies, immune complexes, toxic substances, and abnormal cell populations. As therapeutic efficacy is established, patients with conditions such as thrombotic thrombocytopenic purpura, systemic lupus erythematosus, and myasthenia gravis may have applied researchers to thank for their new treatments.

Many other examples suggest the ingenuity of these medical inventors. A few highlights include:

- A new technique that literally washes diseased cells from the lungs by injecting and then aspirating a sterile solution. Known as bronchoalveolar lavage, it is safe, almost pain-free, and allows physicians to study cell populations and protein content in diagnosing lung disease. It is most useful in differentiating among infiltrative conditions such as asbestosis, sarcoidosis, and hypersensitivity pneumonia.
- An enzyme to change blood types. A specific enzyme converts type B cells to type O cells by removing one of the simple sugars that differentiates the two types. Investigators are now looking for a simple enzyme to change type A cells to type O cells. Because patients can receive transfusions only of type-compatible blood, the

ability to transform donated blood to a needed type will improve blood resources.

- An approach (tested in animal models) to measure blood flow to the heart following a heart attack. An application of positron emission tomography, this method of measurement allows scientists to see a picture of the heart and its circulation. The latter is important because reduced blood flow or perfusion is responsible for the often fatal tissue damage that can occur in a heart attack or myocardial infarction (MI). Methods being developed to improve perfusion during and after MI also may benefit from the ability to assess blood flow more safely and accurately.

Clinical Investigation

Developing and Refining Medical Care Practices

One of every 12 black Americans carries a gene called hemoglobin S (HbS). This gene can transmit sickle cell disease and related hereditary disorders to the children of its carriers. A child born to a couple who both have a sickle cell gene has a 25 percent chance of developing the condition.

In the past 10 years, sickle cell disease has received increasing attention because of the chronic anemia, major organ damage, periodic episodes of debilitating pain, and unrelenting emotional stress it produces.

Clinical investigators have used insights from the basic science of molecular biology and new techniques developed through applied research to produce prenatal diagnostic tests. The opportunity to know if a fetus has this gene is now available to parents who once could only wait and see.

The process of developing these tests is one example of how clinical investigation works—by combining basic and applied research with clinical observation to refine and improve methods for patient care.

Before 1972, there was no way to diagnose sickle cell disease until a child was 6 months old. Based on new knowledge about the kinds of hemoglobin produced by sickle cell carriers, a prenatal test was developed to examine fetal blood samples. The procedure, called fetoscopy, was effective, but it also was costly and caused spontaneous abortion in 3 to 5 percent of women tested.

New molecular technology allowed clinical scientists to develop a different kind of prenatal test. With this method they looked first at the amniotic fluid around the fetus for a series of nucleic acid fragments found to be linked to the HbS gene. The test was often successful but required similar genetic studies of other family members to interpret the findings.

As investigators continued to refine the technique of amniocentesis, they found a way to recognize the mutation of the HbS gene itself in the amniotic fluid cells. This procedure was proven safe in extensive clinical application, and it is now widely available. It does, however, have two drawbacks: It cannot be performed until the 16th week of pregnancy, and test results are not available for 2 weeks.

Once again, clinical investigators are responding. A new diagnostic procedure, known as chorionic villus biopsy, removes small plugs of tissue from the chorionic villi (the hairlike projections of the membrane that surrounds the embryo in early pregnancy). The tissue contains rapidly dividing fetal cells, which are analyzed for a mutation in the DNA sequence. This method is currently

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undergoing the testing for safety and accuracy that amniocentesis has been through. If remaining questions about the technique are answered favorably, it could allow earlier, faster prenatal diagnosis of sickle cell disease.

Because clinical investigation involves transferring new knowledge into medical practices, prenatal diagnosis by DNA analysis has been and continues to be applied to other hereditary disorders. Thalassemia is already diagnosed using these methods, and the cloning of DNA sequences related to a number of other genetic diseases should allow their use to multiply.

Diagnostic methods are not the only focus of clinical investigation. A similar process of defining and refining occurs in developing new drugs and other therapies, new surgical procedures, and new risk factors or preventive strategies.

Answering the Questions About Treatment

Any new therapy or procedure developed by clinical investigators raises questions about its efficacy, long-term effects, and best use. Clinical trials are designed to answer these questions and validate new measures before they are routinely applied in medical practice.

What questions do clinical trials involve? One of the most basic is: Does a new drug or therapy reduce death or illness? The Beta-Blocker Heart Attack Trial, for example, tested the usefulness of the drug propranolol in improving survival among heart attack patients. The trial showed that the drug did reduce deaths by 26 percent and reduced as well the patient's probability of having another nonfatal heart attack.

Clinical trials also compare therapeutic approaches and answer the question: Which kind of treatment is most successful? The Hypertension Detection and Followup Program (HDFP) featured this kind of comparison. It revealed that systematic treatment to bring high blood pressure down to an established goal produces a 17 percent greater reduction in mortality than usual care. The treatment consisted of pairing stepped-care drug therapy with aggressive patient followup, education, and support.

The HDFP also answered another common clinical trial question: Which patients benefit from therapy? Earlier trials had demonstrated the fact that drug treatment reduced mortality for people with moderate or severe blood pressures (diastolic above 95 mm Hg). The HDFP looked at a new group, those with mild hypertension (90 to 94 mm Hg diastolic), to determine benefit. Results showed that systematic treatment reduced mortality even more for the mild group than it did for those with moderate and severe elevations.

A more subtle variation of the "who benefits" question is: Which therapy offers greatest benefit to a particular group? The Coronary Artery Surgery Study is a good example of a trial that answers this question.

This trial compared prompt coronary artery bypass surgery with the strategy of medical management until symptoms dictated surgery for a group of patients with coronary disease and mild symptoms. It showed that both approaches were about equally effective in prolonging life. However, bypass surgery caused a greater reduction in chest pain and a greater improvement in activity level.

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To answer these kinds of questions reliably, a clinical trial is often a large, complex undertaking. The HDFP alone involved 14 clinical institutions and about 10,500 participants to ensure representative, broadly applicable results. It took 9 years from the initial recruitment of patients to measure progress adequately.

In addition, the HDFP's systematic care group received special interventions whereas the usual care group did not. Setting up a test and a control group allowed HDFP investigators to be sure that the reductions in mortality they observed in the test group were a result of the special intervention, rather than of coincidence or an unrelated factor. Because the design of a clinical trial is critical to the validity of its results, scientists pay stringent attention to such details. Thus, while trial results receive the greatest recognition, some of its most important work takes place before the first patient arrives.

The NHLBI worked with Giant Food stores to give shoppers new information on diet and heart health. Shoppers found printed materials, such as this poster, at the point of purchase.

Demonstration and Education

Promoting Application of New Knowledge

A woman in a supermarket knows she should be buying foods that help her family control weight and cholesterol. But when it comes to making real food choices, terms such as sodium content, fiber, calories, and polyunsaturated fat seem like a foreign language.

A hospital in a large city reviews its emergency room records and finds a high percentage of its patients are children with acute asthma attacks. While the hospital tries to cope with the costs, families wonder how to cope with the emotional strain asthma creates in their lives.

A physician treats high blood pressure according to established guidelines. Reading the literature, he finds reports of new antihypertensive drugs, new approaches to dietary management, and new clinical trial results that answer many questions but raise others.

These seemingly unrelated problems have a similar solution—the on-target dissemination of new research findings. The demonstration and education phase of the research spectrum meets this need to get research into the hands of those who can put it into practice.

Although research dissemination projects have many mechanisms, the process usually has four common elements. Information is first synthesized. It then is packaged in practicable formats appropriate to the information, the purpose, and the audience. Finally, it is distributed. Public and private sector groups with an interest in the information often are involved with the NHLBI in formatting and dissemination. These groups complete the cycle by giving the Institute feedback about the new information.

The "Open Airways" program for teaching children with asthma and their families self-management skills was developed by Columbia University through an NHLBI grant. The Institute formatted Columbia's program guidelines into finished teaching tools such as this and is working with the American Lung Association to disseminate the program across the country.

How are demonstration and education efforts helping the woman in the market, those dealing with childhood asthma, and the physician facing an information explosion?

The Institute's Foods for Health Program worked with the Giant Food supermarket chain to help shoppers understand and use new research findings about diet and heart health. Shelf markers, posters, and leaflets pointing to low fat and low sodium foods, health-conscious recipes, and practical meal-planning guidelines were developed cooperatively and then placed prominently in Giant's Washington, D.C., area food stores. In a followup survey, shoppers who used the materials during the 1-year pilot program reported that the Foods for Health information helped them decide to change their eating habits.

Since that time, the "Eater's Almanac" and other program materials have been reformatted, added to, and distributed to shoppers and other audiences concerned with healthy eating; the U.S. Army alone reprinted and distributed 9.5 million almanacs in its commissaries. American Telephone and Telegraph, Johnson & Johnson, the Food Marketing Institute, P&C Foods, and the hotel division of DuPont are some of the major industries and groups involved in disseminating these materials.

The NHLBI is using another mechanism to bring newly tested information about pediatric asthma to communities. Institute-supported research projects in the late 1970's developed and tested new techniques for helping children and their families to cope with and control asthma. The three long-term projects produced educational programs, each targeted for use in a different population or teaching situation. Pilot tests of the programs showed that the courses helped families take more steps at home to manage asthma attacks and to reduce the emotional stress this chronic disease brings. School absenteeism and associated hospitalization and emergency room costs also declined.

Without the Institute's active dissemination, these important results might have been available only through articles in the medical literature or through talks given at professional meetings.

The NHLBI's Division of Lung Diseases and the Office of Prevention, Education, and Control, however, developed an active outreach effort that began by formatting the three educational programs into concise, easy-to-use teaching tools. The American Lung Association (ALA), which itself had asthma education materials, agreed to collaborate with the NHLBI. Together, they developed a model workshop to introduce the educational programs to local health facilities, practitioners, schools, and other

groups that might sponsor them. After several rounds of pilot testing, the workshops and supporting materials will be made available to communities nationwide through the ALA. In addition to offering an appropriate network for dissemination, the ALA also is providing partial financial support for the project.

One of the Institute's most important educational functions is stimulating recommendations for medical practice based on new research to help physicians synthesize the variety of new information that appears in the literature. In a process called consensus development, experts from around the country meet to decide how new, complex, or conflicting findings might affect clinical practice.

Because new information about high blood pressure has increased substantially in the past decade, a series of expert panels have been convened to update medical management guidelines periodically. Panel members represent the major professional and health organizations involved in high blood pressure control—groups such as the American Heart Association, the American College of Physicians, the American Medical Association, and the American Nurses Association.

In 1984, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC) suggested a number of new directions for high blood pressure control. The committee gave recommendations for using the many new drugs and new types of drugs developed since the 1980 JNC, for example. It introduced the concept of carefully monitoring those with "high normal" blood pressure, the 85 mm Hg to 89 mm Hg diastolic range that population studies show carries an increased risk for heart disease, and elaborated on the best uses of nondrug therapy.

Once a consensus report was agreed on, the groups represented on the panel cooperated in disseminating it to their members. In 1984, more than 100,000 reports were distributed this way.

This network of organizations is more than a conduit for information. The broad representation throughout the process ensures that JNC recommendations are credible and accepted. Gaining audience acceptance of new information is a critical step in reaching the goal of demonstration and education activities—practical application.

From Theory to Practice to Theory

The biomedical research spectrum represents the varied activities that make up the NHLBI's scientific process. In practice, however, the progression of knowledge is much less a linear move from theory to practice than the diagram suggests.

A critical feature of the scientific method is the potential for every stage in the process to produce new theories and suggest the need for additional new facts.

Referring to science as a whole, the philosopher Alfred North Whitehead said that the method of invention was the greatest invention of all. Because the biomedical research method does not always proceed in straight-line fashion, it may sometimes seem mysterious. The dynamism and diversity of the process itself, however, has allowed heart, lung, and blood medicine to make the lifesaving progress demonstrated in the past decade. Lewis Thomas calls this complex, interrelated process "the most powerful and productive of things human beings have learned to do together."

Many people tend to envision a medical "breakthrough" as something that happens if not literally overnight, at least very close to that: a culmination of steady technological progress coupled with the sudden insight of a single brilliant medical researcher. But scientists know better.

The first successful transplant of a human heart from one body into another, performed by Dr. Christian Barnard in 1967, was the subject of round-the-world headlines. Behind that dramatic event, however, were years of animal experiments as well as years of experience in transplanting human kidneys. Such surgery had been attempted as far back as the 1940's, and the first wholly successful kidney transplant took place in 1954 at Peter Bent Brigham Hospital.

Organ transplants—indeed, almost all modern surgical procedures—would not be possible without today's highly controllable anesthetics, infection-preventing antibiotics, and advanced surgical techniques. Surgery itself has evolved over centuries of trial and error and, in turn, has been inherently dependent upon intimate knowledge of human anatomy. That knowledge can be traced directly to the pioneering work of the Flemish physician Andreas Vesalius, who in 1543 published his definitive *De Corporis Humani Fabrica* (On the Structure of the Human Body), the very first accurate work on the subject. It was the same year in which Copernicus published a revolutionary volume asserting that the Earth orbits the Sun, rather than the reverse.

Vesalius was engaged in basic research—research directed toward greater knowledge or understanding. Sometimes that leads to applied research, which suggests ways for putting the knowledge to practical use. Sometimes many other steps intervene, as between Vesalius' careful mapping of the human interior and Dr. Barnard's transplant of the human heart. Such a venture was beyond the dreams of Vesalius, who sought only to understand and describe the body's structure.

This synergy between basic and applied research, the unpredictable and the planned, is fundamental to scientific research in general and to biomedical research in particular.

Basic Research

The Unexpected Uses of New Knowledge

In 1977, Julius H. Comroe, Jr., M.D., and Robert D. Dripps, M.D., published a now-classic study which was, essentially, "research on research." In it, they traced the key developments behind major advances in the areas of cardiovascular and pulmonary medicine—the heart, circulatory system, and lungs—over the previous three decades. Of the studies that produced major clinical advances, almost one-half focused on topics totally unrelated to the eventual "breakthrough."

Examples of such scientific serendipities arise for many kinds of discoveries that now help control and prevent heart, lung, and blood diseases.

- Echocardiography, an ultrasound technique used in the diagnosis of heart problems such as mitral valve disease and cardiac enlargement, had two inadvertent precursors. Naval research found that sonar devices using reflected sound waves could detect submarines under water. A study of the way in which bats, flying at top speed in the darkness, catch tiny in-

Testing for Rh factor in the blood, knowledge of which allows accurate blood typing for transfusions.

An understanding of the Rh factor was derived from a study on the variations in color of butterfly wings.

sects also elucidated ultrasonic echoing mechanisms.

- Heparin, an anticlotting agent that prevents thrombosis and is indispensable to successful open heart surgery, was discovered by a Johns Hopkins University medical student. He was working on a basic biochemistry problem on factors favoring coagulation of blood.
- Cardiac catheterization, another important diagnostic tool for evaluating heart disease, was developed by two pulmonary physiologists who wanted to learn more about how blood and air are distributed to air sacs in the lungs. Some years later these scientists and others applied the technique to assess patients with specific congenital heart defects.
- The discovery of the Rh factor in the blood allows accurate blood typing for transfusions and ensures safer childbirth. It derived from a study on the variations in color of butterfly wings.
- Hypothermia, or body cooling, which is a technique necessary for successful heart surgery, was made possible in part by a study of the causes of torpidity in the tenrec. Researchers found that the tenrec, a tropical animal, could be made to hibernate in winter months by slightly decreasing its body temperature.
- X-rays, which are used in diagnosing all kinds of heart, lung, and blood vessel diseases, were discovered by basic scientist William Roentgen. He was studying the electrical nature of matter when he found that x-rays from a Crooke's tube could pass through the human hand and darken a photographic plate.

Many Discoveries = A "Breakthrough"

The Comroe-Dripps study also made another interesting point. Not one of the advances they investigated was the result of a single breakthrough by a single brilliant scientist. Each depended on trails blazed by others.

One such advance was the conquest of childhood rheumatic fever—once a common crippler that turned formerly robust youngsters into frail invalids. Since the 1960's, the disease has been vanishing from the United States although it remains a major problem for underdeveloped countries. Comroe and Dripps tracked that conquest back to the first observation, in the late 19th century, that the disease did in fact involve the heart—although not until after 1900 was the precise nature of the heart lesion pinpointed. Still, its cause was unknown, and no connection was made with infection.

Without the development of microscopes and without Leeuwenhoek's discovery of the existence (though not the mischief) of bacteria, the bacteria that cause disease would not have been isolated. (The bacterium of leprosy—the first—was isolated by Hansen in 1874.) Pasteur contributed the idea of conferred immunity. In our own century, the ubiquitous bacteria known as streptococci were identified and analyzed (one strain had been isolated in the 1880's). The advent of antimicrobial agents—the sulfas and penicillins—occurred in the 1930's, although large-scale production of antibiotics did not take place until the next decade. Also in the 1930's came the realization that there was a relationship between streptococcal infection and rheumatic fever, and finally, it was perceived that if streptococcal throat infections were effectively treated with antibiotics, rheumatic fever—which may be a sequel to

18

such infections—could be totally prevented.

Is this always the way research works? While exceptions exist, the complex pathways to discovery portrayed in the Comroe-Dripps study hold true for many of the key clinical advances of the 1970's and 1980's. The following three accounts illustrate how the nonspecific and sometimes unrelated results of basic research—and the planned application of new knowledge to specific problems—worked together to prevent hepatitis, treat respiratory distress syndrome in infants, and establish the role of cholesterol as a risk factor for heart disease.

The Fight for a Baby's Breath

Little Lungs, RDS, and Dr. Liggins' Lambs

In November 1963, most Americans of every political persuasion found themselves reaching out emotionally to the young widow of President John F. Kennedy. In the shock of that devastating, violent loss, few remembered that Jacqueline Kennedy had, in fact, been twice bereaved; her second son, Patrick Bouvier Kennedy, had died earlier that year.

The Kennedy infant was one of an estimated 25,000 newborns who succumbed in 1963 to a condition still known by the purely descriptive phrase "respiratory distress syndrome"—RDS for short (sometimes abbreviated NRDS, "N" for "neonatal," pinpointing the specific incidence of the syndrome). Mainly as a result of technological advances in neonatal care, fewer now die, but the syndrome is still responsible for some 10,000 infant deaths in our country each year.

Prematurity is the number one cause of newborn deaths. A premature birth is one that occurs before nature intended, the unexpected entrance of an infant into the outer world when that child still needs the nurturing environment of the womb. Among premature infants, RDS is the number one killer; and RDS develops in 1 in every 100 live births.

In RDS, a baby's lungs have not developed sufficiently to sustain life outside the womb. Even if the infant, with breathing assistance and round-the-clock intensive care, survives that crisis, the oxygen deprivation can lead to lasting consequences, including brain damage. Thus, there have been constant efforts to predict the syndrome, to improve treatment, and most of all to prevent RDS entirely.

Predicting RDS

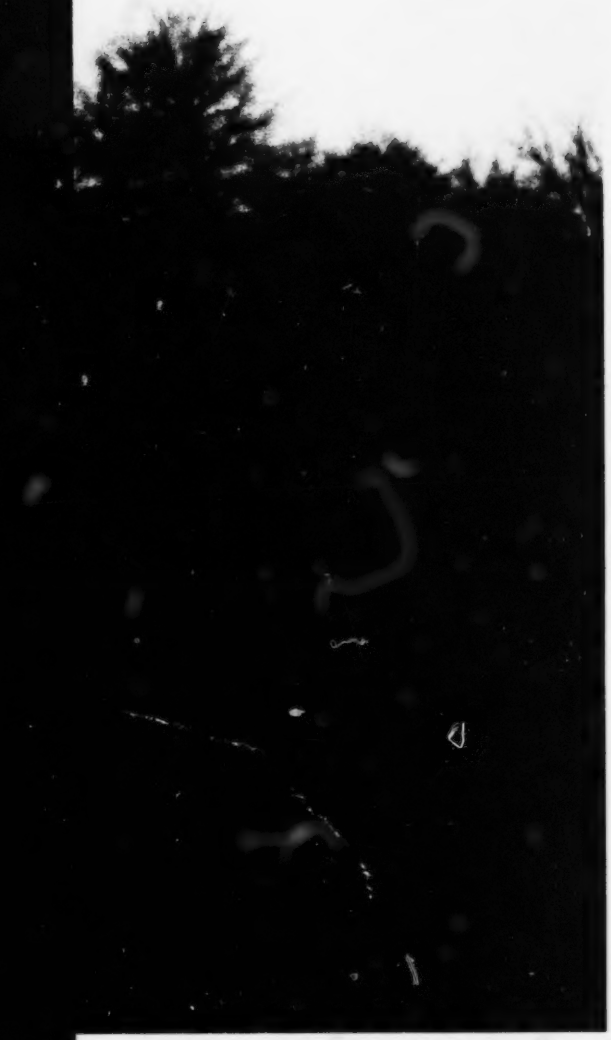
Physicians do have a better understanding of the basic problem than they had two decades ago, an understanding derived mostly from autopsy examination of RDS's tiny victims. In the mature lung, a fluid known as surfactant is present. This liquid, which regulates surface tension within the lung, is essential to the opening and closing of the alveoli, the tiny air sacs, so that they can effect the oxygen-carbon dioxide exchange necessary for life. The result in RDS is that after a single breath, the lungs—almost like sponges that have been squeezed dry and not released from the grip—fail to expand or expand insufficiently (the severity of the syndrome varies).

Predicting the likelihood of this disorder is helpful because such a rescue effort requires both special equipment and experienced personnel—physicians and nurses expert in dealing with these fragile infants. If the risk can be foreseen, the rescue team

Seemingly unrelated research on the adrenal glands of sheep was the key to a new drug for preventing neonatal respiratory distress syndrome (NRDS).

can be standing by before the baby's birth. It is also sometimes possible to delay the imminent birth, in hope of buying some precious lung-maturing time.

In the late 1960's, researchers at the University of California, San Diego, found a way to detect the level of lung maturity before birth. Elements of surfactant, they found, were present in the amniotic fluid surrounding the fetus, but there was a change when the fetal lungs had reached maturity. At that point, the levels of a phospholipid called lecithin rose in relation to another phospholipid called sphingomyelin. By using



amniocentesis (inserting a hollow needle through the mother's abdomen and into the fetal sac and withdrawing a sample of the amniotic fluid), the physician can determine the level of lung maturity. When there is evidence of immaturity, the health care team can attempt to postpone the birth until repeated sampling shows a lecithin/sphingomyelin ratio that signals maturity, as well as prepare for the treatment of an infant with RDS in case those delaying tactics fail.

Improving Lung Maturity

Major attention in the area of prevention has focused on quite another part of the body, seemingly not intimately connected with the lungs or their function—the pair of endocrine glands, located in the upper abdomen just above the kidneys, called the adrenals. Interest in them stemmed from two unconnected observations that occurred, quite literally, a world apart.

Scientists at Pennsylvania State University reported in early 1972 on autopsies they had performed on 387 infants who had survived for less than 3 days; 220 had died of RDS, the rest from other causes. All the organs were carefully weighed, measured, and examined and, in the course of that scrutiny, pathologists found something quite unexpected: The adrenal glands of the RDS infants were 19 percent (nearly one-fifth) lighter than those of the other infants.

Meanwhile, in Auckland, New Zealand, in research unrelated to RDS, investigators led by Dr. G.C. Liggins were studying the relationship of the adrenal glands to the onset of labor—not in humans but in sheep. Injecting the unborn lambs with adrenal hormones, they discovered, induced premature delivery. They also found, again entirely unexpectedly, that some of the lambs survived even though they were born as early as 118 days after conception (the normal gestation for sheep is 147 days). That news sparked new thinking on the part of two North American research teams.

At Johns Hopkins University in Baltimore,

investigators set out to test the possibility that lung maturity might have made the difference for the surviving lambs. Using ewes carrying twins, they injected just one of each fetal pair with adrenal hormones. In all cases, the lungs of the treated lamb turned out to be more mature than those of its twin.

At McGill University in Montreal, pediatricians were also intrigued by Dr. Liggins' lambs, but they wondered if the phenomenon were confined to sheep. They decided to find out by experimenting with a different animal, the rabbit. Singling out one or more fetuses in several pregnant rabbits for hormone injection, given on the 24th day of gestation (normally 31 days), they removed the fetuses for examination 2 or 3 days later. The lungs of the injected fetuses were "approximately twice as mature" as those of their littermates. Injected rabbits survived, on the average, four times longer than their untreated siblings. Microscopic examination of the lungs of the treated rabbits revealed heightened cellular maturity and, significantly, pulmonary surfactant that had, as they put it, "appeared ahead of schedule." When lungs from those fetuses were removed and experimentally inflated, they were found capable of holding more air.

The hormones in question are known as corticosteroids, often referred to popularly in the singular, "cortisone." They are produced by the cortex, or outer layer, of the adrenals. The one secreted in humans is called cortisol, and there are many natural and synthetic forms and variations, which are used in the treatment of a variety of conditions, including deficiency diseases as well as rheumatoid arthritis and other autoimmune disorders (in which the hormones suppress inflammatory reactions).

The New Zealand scientists went on to apply the therapy to humans, giving hormone injections to pregnant women before the advent of premature labor. By the mid-1970's, U.S. investigators were showing increased interest. A team at Boston Children's Hospital Medical Center pointed out that the cortisol levels in amniotic fluid generally rise at about the same time as the lecithin/sphingomyelin ratio and that infants delivered vaginally have higher blood levels of the hormone than those delivered by cesarean section—suggesting that higher cortisol levels are normal, perhaps even necessary, accompaniments of labor.

Long-Term Effects

Still, there were questions, relating specifically to a fundamental tenet of medicine: *Primum non nocere*, "First of all, do no harm." What untoward effects might hormone administration have on mother and child?

In 1976, under the sponsorship of the NHLBI's Division of Lung Diseases, a 7-year trial was begun, designed to answer three questions: (1) Would adrenal hormones injected in mothers-to-be reduce the incidence of RDS in their babies? (2) Would there be short-term adverse effects on mother or child? (3) Would there be adverse effects on early childhood growth and development? The research took place at five university medical centers in the United States and Canada and involved nearly 700 women at risk for premature delivery in whom testing showed that fetal lungs had not yet reached maturity. The women were randomly assigned to receive either the corticosteroid dexamethasone or a look-alike inert liquid.

There were no ill effects on the mothers or on the newborn infants. The children

22

who survived and were not lost to followup (more than half were still available at the age of 3 years) were evaluated at 9, 18, and 36 months. No deficiencies were found in those children whose mothers had received the hormone; in fact, their height and weight were slightly greater than those of the children of the untreated mothers. There were also more respiratory infections reported by parents of children in the placebo group during the first 1½ years.

As to the primary question of whether the intervention was beneficial, there were two surprises. One was unquestionably a bonus "side effect": There was a much lower rate, among the infants exposed to dexamethasone in the womb, of a severe intestinal disorder called necrotizing enterocolitis. This condition occurs most often in premature infants, afflicts an estimated 4,000 babies in the United States each year, and has a mortality rate of 30 percent.

But the main surprise was the selectivity of the beneficial effects of treatment. Overall, the incidence of RDS in the treated group was reduced by one-third in comparison to the placebo group. But that effect did not occur across the board. In the few cases of multiple births, the hormone had been of no help at all. Nor were there any appreciable benefits to male infants; the promising decrease in problems was due almost entirely to beneficial effects on single female fetuses. Reflecting normal patterns, a little over one-half of the mothers in both the hormone and placebo groups gave birth to sons. Among the boys, slightly more of those in the steroid group (14.9 percent) had RDS than in the placebo group (14.1 percent); but for the girls, the figures were 18.8 percent for daughters of untreated mothers and only 4.8 percent for those of mothers who had received the hormone.

Further, there were racial differences. The RDS figures for whites were: Placebo group, 19.7 percent; treated group, 16.7 percent. The results for blacks were: Placebo group, 9.8 percent; treated group, 4.3 percent. Figures for "others," who included both Hispanics and American Indians, were: Placebo group, 28 percent; treated group, 6.4 percent. This represented a dramatic RDS-incidence reduction of more than 77 percent.

Clearly, the trial demonstrated the desirability of dexamethasone administration in potential RDS cases, at least for girls, and especially nonwhite girls. This limited application has the potential to prevent perhaps 15,000 cases annually. But why the differences? The question has sent the baffled scientists back to basics. Clearly, much remains to be learned about the roles that hitherto unsuspected factors, including sex hormones and genetic influences, may play in RDS.

These twins, seen here at age two, were born prematurely and developed respiratory distress syndrome. As a result of NHLBI-supported studies, they received lifesaving treatment that allowed them to enjoy a normal, healthy childhood.

Turning to Primates

Researchers have realized, too, that relatively little is actually known about the course of prenatal development, despite the revelations of such sophisticated technology as amniocentesis and ultrasound. Part of the reason for this lack of knowledge, of course, is that interrupting human pregnancy solely for the purpose of fetal study would be unthinkable. Thus, biomedical scientists seeking answers turn to animals, especially to subhuman primates, since they are physiologically closer to humans than, say, sheep or rabbits.

Since prematurely delivered baboons develop a respiratory distress syndrome much like RDS in humans, baboons are currently

A scanning electron micrograph of a macrophage (large mass at bottom). Researchers believe these large white cells may play a role in the NRDS disease process.

providing an excellent model for RDS researchers. Studies of monkey fetuses at various stages of pregnancy are providing new insights about the development of the circulation, muscles, and nervous-system activity that may, it's now suspected, have some bearing on the cause of RDS.

The dexamethasone questions are also being pursued in the model monkeys. Experiments are now under way to determine exactly how the hormone is optimally passed from mother to fetus and just how it acts, or does not act, on the fetal lung. The animal trials have already shown that when the hormone is effective, it not only speeds surfactant synthesis but also increases lung inflatability, just as scientists observed in the rabbits more than a decade ago. How this occurs is not yet known. Nor is it known why, in the animals, antenatal hormone treatment is effective mostly in male offspring, in a complete reversal of the results in the human trial. Still another hint of a new research path has arisen in the possible role of macrophages, which are large "scavenger" white cells whose normal function in the body might be described as patrolling the internal environment and trucking off litter—cellular debris resulting from the destruction of invading organisms as well as the continuous discarding and replacement of worn-out cells. Premature infant monkeys with RDS have few such macrophages in the alveolar sacs of their lungs; animals without RDS have a great many more. What role they play, and how their numbers relate to RDS, is still a mystery.

Blood Barriers That Shortchange the Heart

Cholesterol and the CPPT

Cholesterol is a substance with a split personality. Secreted by the liver and stored in the gallbladder, it plays a major role in digestion as an active constituent of bile. (Its name, coined from two Greek words, simply means "bile solid.") But it can also prove to be a major troublemaker. It coalesces to

form gallstones and, in its most infamous guise, joins with other substances in the plaques that occlude the arteries, including those supplying the heart itself. It thus contributes to the devastating event technically termed myocardial infarction and known familiarly as a heart attack: A death of heart-muscle tissue due to failure of oxygen supply.

The role of cholesterol in this process was not defined overnight. Two decades ago, there was a strong suspicion that elevated cholesterol levels in the bloodstream contributed to coronary heart disease. But suspicion is not proof. Nor had it been demonstrated that lowering the level of blood cholesterol—if, indeed, that was possible—could prevent heart attacks. Nevertheless, by the mid-1960's many physicians began to advise their patients to go easy on dietary fats, especially the forms known as saturated fats, which seemed likely to foster high cholesterol levels.

Over the next few years, there were many anecdotal reports, as well as tales of trials conducted on small groups of patients, showing that lowering of serum cholesterol could be achieved in some by diet, in others by drugs (several have been introduced over the last two decades), and in most by a combination of the two. But would that really prevent heart attacks? No one could tell from tests on one patient or even a fairly small group, because the findings might be skewed by other factors and concurrent risks. What was needed was a very large cohort of test subjects drawn from a number of geographical areas.

Constructing a Conclusive Test

The Coronary Primary Prevention Trial (CPPT), sponsored by the National Heart, Lung, and Blood Institute, was launched in 1973, with 12 participating university research centers in the United States and Canada. The subjects of the study were about 3,800 men with higher-than-normal blood cholesterol (medically, hypercholesterolemia). They ranged in age from 35 to 59 and as yet had no evidence of heart disease. The study was limited to men, because men have been shown to be far more susceptible to heart attack than women.

All the subjects were placed on moderately low-fat diets and were randomly assigned to one of two groups. One group was given the cholesterol-lowering drug cholestyramine, the other a placebo. Cholestyramine was selected because it was known to be low in side effects and because it lent itself easily to devising the placebo, which is an inert substance used in clinical trials and specifically concocted to be indistinguishable from the active medication being assessed. The trial was double-blind, a hallmark of scientific respectability in any such research involving a medication. Neither test subject nor physician knew whether the "medicine" was the test medication or the dummy drug, thus eliminating any effects due to biases, hopes, or expectations on the part of physicians or patients. Each of the 3,806 participants was followed and tested for a minimum of 7 years; those who had neither died nor experienced a heart attack, stroke, or other evidence of cardiovascular disease were followed for a full decade.

The result, announced in January 1984: 32 deaths from coronary heart disease occurred among those who had received the real drug; but 44, or 37.5 percent, more

deaths occurred among those who had taken the placebo. Importantly, there were no differences between the two groups in other presumed risk factors such as smoking, exercise, weight, or alcohol consumption. While both groups lowered their blood cholesterol (showing that diet alone can achieve some improvement) the figures fell significantly lower among those taking the drug.

The calculated reduction in deaths from coronary heart disease as well as nonfatal heart attacks in the diet-plus-real-drug group was 19 percent, nearly one-fifth. Further, when the risk was analyzed in relation to the degree of reduction in the serum cholesterol level, the researchers found that a 25 percent reduction in blood cholesterol level meant a heart attack risk reduction of 49 percent. This decline represents a 2 percent risk reduction for every 1 percent drop in serum cholesterol.

Strictly speaking, the results of the research apply only to those who fit the description of the test subjects—middle-aged males with substantial elevation of blood cholesterol. But the participating scientists feel that results are probably applicable to females as well as younger people of both sexes.

Back to Basics

While the CPPT has borne out a long-held hypothesis and will doubtless spur a great deal of applied research, much still remains to be learned about the physiological process of atherosclerosis, the occlusion of key arteries by obstructive lesions. While drug researchers are seeking improved agents, basic scientists are returning to the body itself to find clues to the atherosclerotic process. Paths currently being pursued:

- Platelets, also called thrombocytes—the blood's clotting cells—seem to play a role in atherosclerotic plaque formation. Platelet-derived growth factor, which is secreted by the platelets, appears to stimulate the proliferation of small muscle cells to form the plaque. The question: How?
- Prostaglandins appear to be involved. These "minihormones," produced by many if not most of the body's tissues, have a bewildering repertoire of varying, often counterbalancing, effects. They raise or lower blood pressure, incite or discourage inflammation, constrict or relax the bronchial tubes. Some apparently have a major impact on the dilation and contraction of arterial walls, as well as on platelets. The question: What?
- Collagen, a fibrous connective substance that is a constituent not only of muscles and cartilage but of binding tissues throughout the body, may also be involved. It was previously viewed as an inert framework binding fatty atherosclerotic lesions to arterial walls. Those delicately interlaced cages can apparently remain in place and act as mechanical obstructions to blood flow, even if the lesion's fatty components have been dispersed. The questions: How and why?
- Aside from clear patterns of familial hypercholesterolemia, some people appear to be more prone than others to adverse effects of high serum cholesterol levels; some with such levels, in fact, appear to be genetically protected. The question: How?

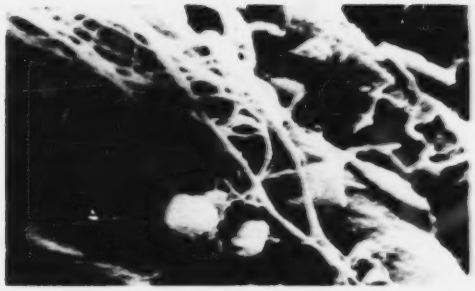
26

The Saga of "Serum" Hepatitis

Outbreaks of hepatitis, with its wasting, debilitation, and characteristic yellowing of the skin and the whites of the eyes (jaundice), occurred as early as the fifth century B.C. "Campaign jaundice" ravaged armies in the Middle Ages. The disease struck the ranks of George Washington's Delaware Regiment and disabled some 70,000 Union troops during the Civil War. And it is still very much with us today; some 57,000 cases were reported to the U.S. Centers for Disease Control (CDC) in 1983. As with a great many diseases reported to the CDC, recorded cases unquestionably represent only the tip of the proverbial iceberg.

By the early 20th century, with the discovery of the viruses responsible for yellow fever and other ills, scientists began to suspect that hepatitis, too, might be triggered by one of these tiny organisms. By then it had been observed, too, that the disease seemed to take two distinct forms. One form ran rampant under unsanitary conditions, such as those of military encampments where food was carelessly handled and sewage flowed unchecked. It was clearly contagious, and it came to be known as "infectious" hepatitis.

The other form of hepatitis apparently entered the body only through the bloodstream. Outbreaks had been traced to smallpox inoculation programs, later to clinics treating diabetes with injected insulin. It was (and is) far more lethal, with a death rate of 5 to 10 percent; it came to be known as "serum" hepatitis. By the 1960's, serum hepatitis was perceived as a major threat to those suffering from illnesses and injuries requiring blood transfusions; hepatitis-contaminated blood could be a killer, not a lifesaver. By the end of that decade, however, new hope had arisen, not only for protecting transfusion recipients but also for preventing the illness in the first place.



Scanning electron micrograph of a blood clot forming at the site of an injury to an animal aorta. A layer of platelets (small spheres) is replacing the surface cells. Scientists believe platelets may play some role in atherosclerotic plaque formation, interacting at the cellular level with the walls of arteries.

The Role of Antigens

That hope stemmed from a purely fortuitous event, quite unconnected with any thought of conquering hepatitis—a 1963 discovery by scientists working at the National Institutes of Health. They were engaged not in seeking the cause or cure of a disease but in studying genetic variations in the blood of populations around the world by looking for various antigen-antibody reactions. Antibodies are produced by the body in response to invasions by "foreign" organisms, which might be infectious agents such as viruses or bacteria, or simply alien tissue incompatible with those of the recipient and therefore "rejected." Antigens can be described as biochemical "flags" carried by such invaders, identifying them and signaling their presence to the immune system. They trigger antibody production, which might be helpful (as in warding off an infection), or distinctly unhelpful (as in rejecting a transplanted organ or transfused blood).

The investigators found that a serum sample from an American hemophilia patient who had received a number of blood transfusions contained an antibody that reacted against something in a serum sample from an Australian aborigine. Since antibodies are produced only after encountering a particular antigen, the scientists reasoned that somehow the American hemophiliac had previously been exposed to the substance in the aborigine's blood, which the researchers dubbed "Australia antigen," or "Au antigen."

27

Using a hemagglutination test, a technician screens blood intended for transfusion for hepatitis B virus. This testing has dramatically reduced posttransfusion hepatitis.

They set out to search for this mysterious substance elsewhere, and their quest was rewarded. It turned up not only in Australia, but in serum from many other people all over the world. One finding seemed to be consistent, substantiating the assumption that the Au antigen was a genetic marker, like the Rh factor, found in some people but not in others. A person who tested positive for Au antigen on one occasion tested positive on other occasions as well, and negative Au antigen tests remained Au negative—just as type A blood remains type A, type B remains type B, and so on. But in 1966, that tidy pattern collapsed.

In that year, the physician-scientists routinely retested a patient who had tested negative before. They were startled to find that the man now tested positive for Au antigen. The researchers had no inkling that they were on the verge of a momentous discovery, that they were about to unearth a medical Rosetta Stone. Because the patient apparently had developed a "new" protein, and since many proteins are produced in the liver, they proceeded typically and performed a series of liver chemistry tests.

Preventive Screening

Those tests showed results highly suggestive of hepatitis. The diagnosis was confirmed by liver biopsy. And by the end of the year, the researchers, now focusing on blood tests of known hepatitis patients, were firmly convinced that the Au antigen was connected with the disease and might even be the cause of the illness itself. Other investigators confirmed these findings and, while the precise role and identity of Au antigen were still unknown, the possibility of one preventive step seemed strong enough to proceed clinically, and blood intended for transfusion began to be screened for the antigen. At Philadelphia General Hospital, one of the first to institute a screening program, the posttransfusion hepatitis rate had been cut by two-thirds by the early 1970's. An assay kit was developed and approved for commercial distribution in 1972, and the testing soon became routine throughout the United States and many other countries.

By the early 1970's it was clear that the two forms of hepatitis were in fact two distinct infections, and since both were infections, the previous labels were less than accurate. "Infectious" hepatitis was renamed hepatitis A, and "serum" hepatitis became hepatitis B. Au antigen was associated only with the latter. (Hepatitis caused by neither the A nor B virus was soon called hepatitis C, but since it is not clear how many viruses may be involved, a nonidentified hepatitis virus is now termed "non-A, non-B.")

It was becoming apparent that mere screening of blood to be used for transfusions was not enough. Transmissions through a number of routes far from transfusion territory were being rapidly documented. The hepatitis B virus (HBV) can make its way into the bloodstream from needles used by earpiercers and heroin addicts, by acupuncturists and tattoo artists, and by technicians giving children TB tests. It can be carried by the bites of mosquitoes, bedbugs, and human beings. It can even eschew a direct route, moving from person to person via the placentas in pregnant women, breast milk, sexual intimacies, and shared toothbrushes. And an estimated 0.5 percent of the U.S. population, 1 in 200, are positive for Au antigen. They are carriers of the virus (although they themselves may not be ill) and may infect others.

28

The Au antigen is not identical with HBV; the virus itself has now been identified as an organism first observed by a British researcher (dubbed, before its true nature was established, "the Dane particle"). The Au antigen is merely a substance forming a part of the protein coating of the viral particle itself; it is now called HBsAg, for hepatitis B surface antigen. Knowledge of HBsAg allowed scientists to develop a brand new kind of vaccine.

The Vaccine

It was soon found that a preparation purified from plasma containing HBsAg, while incapable of causing disease, could nevertheless confer immunity by inducing in the recipient production of antibodies that would effectively fight the whole virus. (Other vaccines use small quantities of actual virus, whether live or killed.) After successful tests in animals, small clinical trials in humans were attempted, and they, too, proved successful. Next, the first tightly controlled, broad-based trial of the vaccine in humans was launched. The results of that trial, supported in part by an NHLBI grant, were reported in October 1980 by a team from the New York Blood Center. It had been established that the vaccine could reduce the incidence of hepatitis B by over 90 percent. And since there is an apparent connection between a highly lethal liver cancer and prior HBV infection, it may reduce the prevalence of that malignancy as well. The vaccine received licensing approval from the Food and Drug Administration in late 1981 and became generally available the following year.

While the HBV vaccine is both safe and effective, it is not cheap. The antigen must be isolated from pooled plasma collected from carriers and exhaustively purified and safety-tested. Each batch of the vaccine must go through that lengthy and expensive process. Now under study are ways to employ genetic engineering techniques to produce a possibly cheaper vaccine by coaxing a yeast to produce and clone a substance biochemically equivalent to HBsAg.

Scientists are now on the threshold of conquering two major killers—the most lethal form of hepatitis, and a tumor that is one of the most malignant known. Yet this giant step began with a small stumble over a surprising laboratory finding more than two decades ago. Whether these strides might have been made had someone set out deliberately to do so is an unanswerable question. Dr. Baruch S. Blumberg, the head of the NIH team that discovered the link between the Au antigen and hepatitis, received a Nobel Prize for the work in 1976. But as Dr. Blumberg told his Stockholm audience in accepting the award, he and his fellow researchers were simply trained scientists following an intriguing set of clues and "had no set views on where this path might lead . . . . From [the circumstances] it is clear that I could not have planned the investigation at its beginning to find the cause of hepatitis B." And, he added, there is a lesson for the future: "This experience does not encourage an approach to basic research that is based exclusively on specific goal-directed programs for the solution of biological problems."

[redacted]

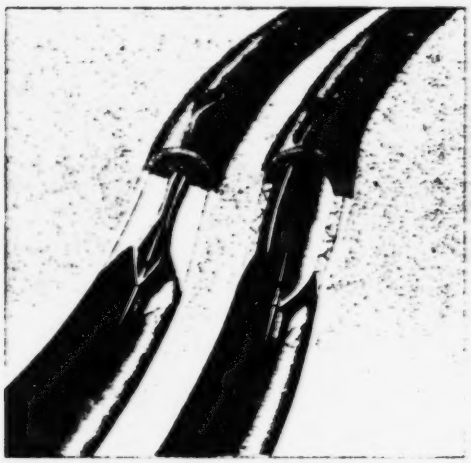
The heart, lungs, and blood work in synchrony to provide oxygen and nutrients to all the tissues of the body and to remove the waste products of metabolism. Air is inhaled into the lungs; the oxygen it contains diffuses through the membranes between lung tissue and blood vessels into the plasma and then into the red blood cells (erythrocytes) where it binds with hemoglobin. The oxygenated blood returns through the pulmonary vein to the heart which pumps the blood to all parts of the body. Once the arterial blood flows into the tissue capillaries, oxygen passively diffuses out of the red blood cells and is replaced by carbon dioxide. The venous blood returns to the lungs, and as it flows through the capillaries of the lung tissue, carbon dioxide diffuses from the blood into the air sacs (the alveoli) from which it is expired and eliminated from the body. This cycle of respiration and circulation proceeds smoothly and ceaselessly in the healthy individual. There are numerous points in this sequence of events, however, where the process can go awry and result in malfunction—a heart, blood vessel, lung, or blood disease.

Coronary Artery Disease

Coronary heart disease, which claimed 555,000 American lives in 1982, can result from atherosclerosis in the arteries that supply blood to the heart muscle. The inner lining of the arteries becomes thickened, rough, and covered with deposits of yellowish plaque that contains cholesterol and other lipid material. As the disease progresses, the inner diameter of the blood vessels decreases and blood flow is slowed or even completely blocked. The plaque becomes fibrous and hardens as a result of mineral infiltration.

Like all muscles in the body the heart muscle, or myocardium, depends upon a continuous supply of oxygen and nutrients for normal function—to beat more than 100,000 times a day—as it delivers oxygenated blood to all the other tissues of the body. Blood is supplied to the myocardium through the network of coronary arteries and its branches. An obstruction in a coronary artery results in ischemia, a deficiency of blood supply to the heart muscle that can cause muscle death, technically known as

Lengthwise section of normal artery compared with blocked artery.



Blocked artery with catheter and deflated balloon in place, left, compared with artery showing inflated balloon pushing plaque against the arterial wall, right.

myocardial infarction. Reversible, temporary ischemia does not cause muscle damage but may cause angina pectoris, pain that occurs upon stress or exertion. Depending on whether the blockage is complete or partial and on the extent of muscle damage, the patient with coronary heart disease can experience angina pectoris that can signal subsequent heart failure, arrhythmias, myocardial infarction, or sudden death.

The symptoms of coronary heart disease can sometimes be controlled with medication. For some patients with coronary heart disease, bypass surgery is recommended. In this procedure, a segment of a blood vessel from the leg is grafted onto the obstructed coronary artery to provide a detour around the blockage.

Recently, a potential alternative to bypass surgery for some patients has been developed and evaluated—percutaneous transluminal coronary angioplasty, or PTCA. In this procedure, a catheter is threaded through an artery in the arm or leg to the clogged area of the coronary blood vessel. A tiny balloon at the tip of the catheter is rapidly inflated and deflated. The pressure of the inflated balloon pushes the deposits of plaque against the wall of the artery and thereby increases the diameter of the lumen, or channel, of the blood vessel so that blood can flow more freely.

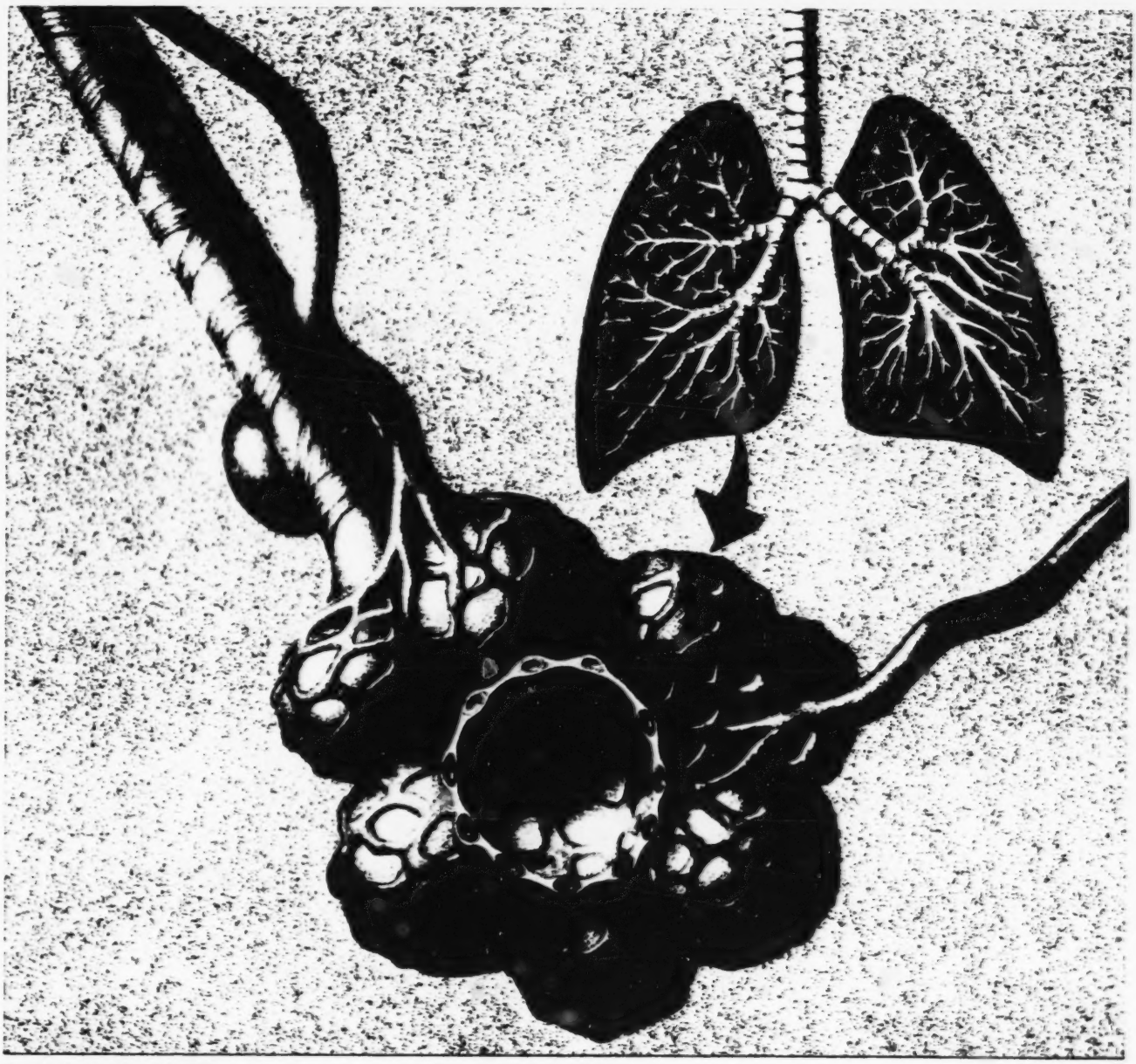
Clinical trials of PTCA have demonstrated an overall success rate of 59 to 63 percent in 1,500 patients from 73 participating centers. PTCA is not without risk, and eligible patients must meet specific clinical criteria. Although not indicated for all patients with coronary artery disease, PTCA offers an alternative to some of those who wish to avoid or postpone coronary bypass surgery.

Emphysema and Bronchitis

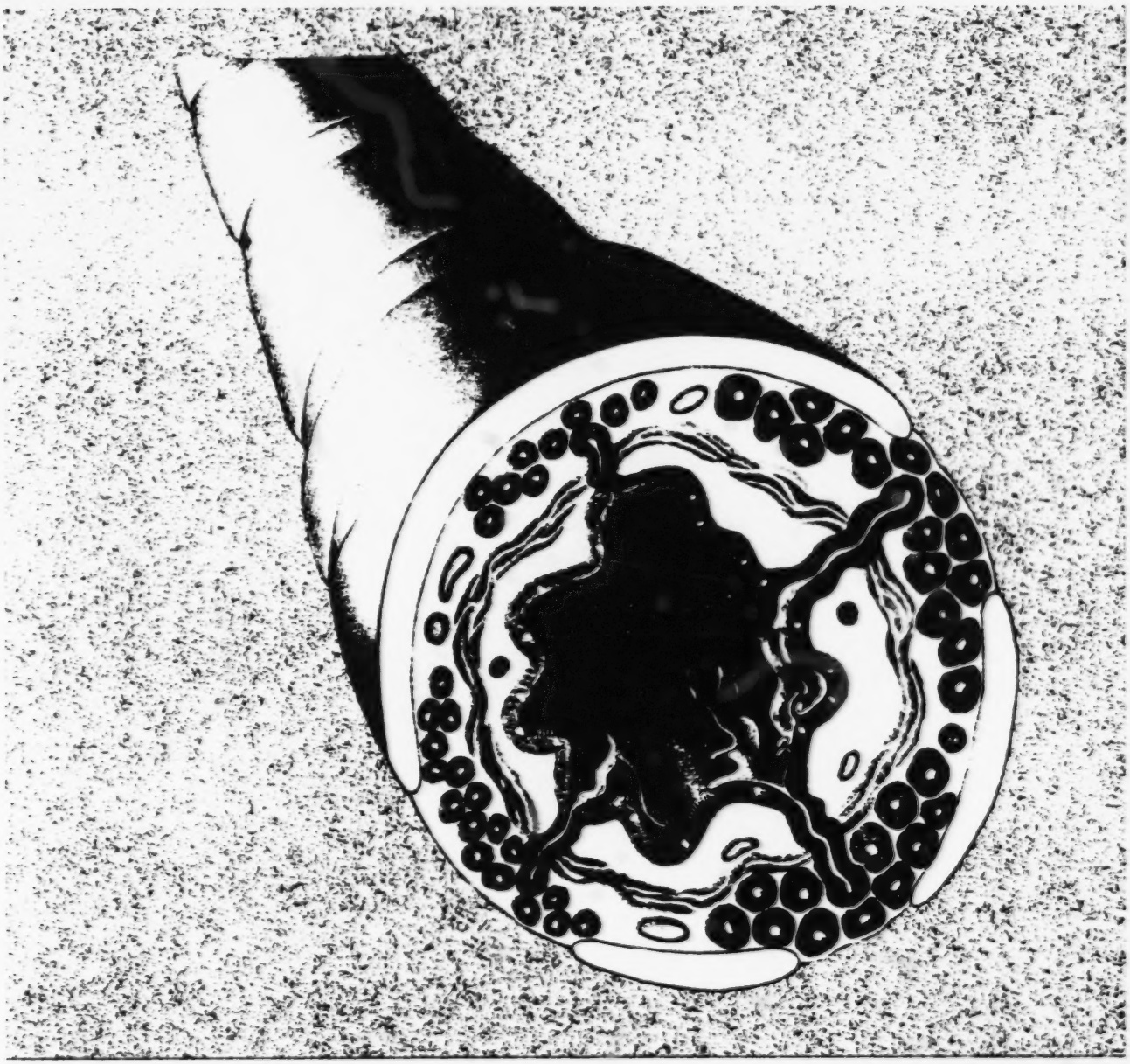
The respiratory tract can be visualized as an inverted tree beginning with the trachea, or windpipe, which branches into two bronchi—one entering each lung. These airways branch into ever smaller airways, the bronchioles, which end in the alveolar ducts from which the air passes into the alveoli, tiny elastic air sacs. The function of this system is to deliver oxygen from inspired air to the capillaries that surround the alveoli. The blood can then deliver the oxygen to all the cells of the body.

At rest, each breath moves approximately 500 ml of air into and out of the lungs. Thus, the healthy respiratory system is able to meet a requirement of 200 ml of oxygen per minute to resting cells. Equivalent volumes of carbon dioxide are eliminated. Under conditions of exertion or exercise this requirement increases up to 30-fold.

Chronic obstructive pulmonary disease (COPD) interferes with this delivery system in two ways: the bronchi become clogged with mucus and destruction of the alveoli occurs. Each causes a diminution of the respiratory system's ability to deliver oxygen to the bloodstream. COPD is the fastest rising cause of death in the country. The term COPD refers to both chronic bronchitis and



Respiratory system showing bronchi, upper right, and enlarged illustration of normal alveolus.



Cross section of normal bronchus showing mucous glands in normal state, *left*, compared with mucus overproduction and edema of bronchial wall demonstrative of bronchitis, *right*.

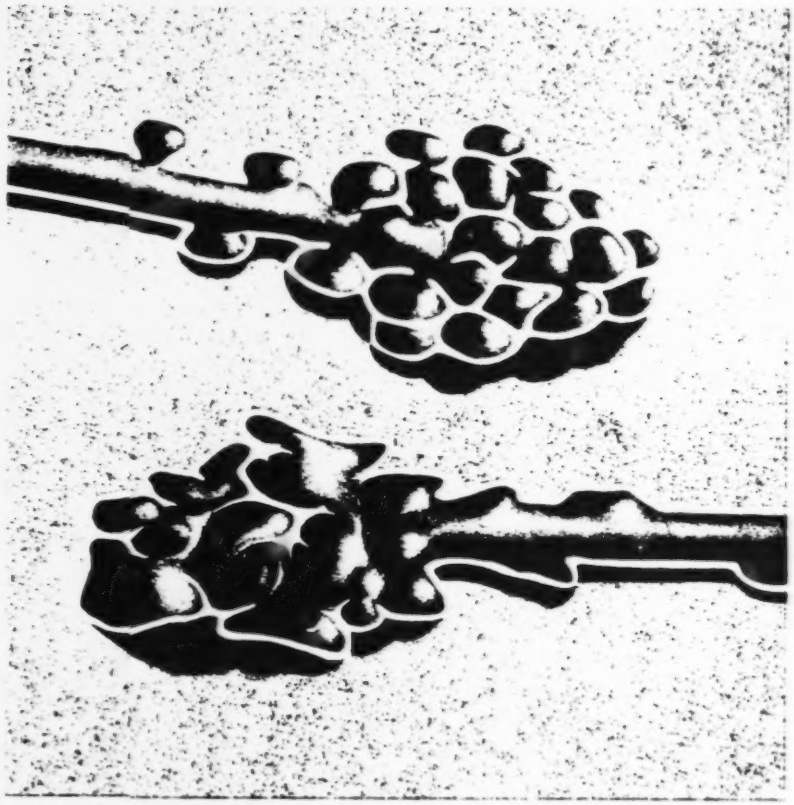
34

emphysema, which usually coexist in varying proportions.

Chronic bronchitis is diagnosed by the presence of cough and sputum production that occurs daily for at least 3 months of each year for more than 2 successive years. The lining of the bronchi contains many mucus-producing glands that serve as a defense mechanism. In response to irritation, these glands produce mucus that ensnares particulate matter. Projections on the cells that line the bronchi, called cilia, sweep the mucus up and out of the bronchial tree. Bronchitis is characterized by multiplication and enlargement of the mucous cells, resulting in overproduction of mucus in the large airways, and by edema and inflammation of the small airways.

The term "emphysema" describes an irreversible pathologic condition of the terminal air spaces of the lung. Normally the 300 million alveoli appear as a honeycomb of elastic, hollow, grapelike structures that branch off the smallest airways. The thin walls of the alveoli are richly supplied with capillaries, and it is here that gas exchange occurs. Their normal elasticity enhances the expiration of air from the lungs. The walls of the alveoli, however, are fragile and susceptible to injury. In emphysema the alveoli become distended and lose their elasticity, and the alveolar walls, or septae, are destroyed. Inflammation and irritation trigger the destructive process. The condition is irreversible, and its progression results in difficulty exhaling air, shortness of breath, and right-sided heart failure.

Researchers have demonstrated that destruction of the alveolar walls is due to an overabundance of a proteolytic enzyme, or protease, called elastase. Normally, the presence of a protease inhibitor, alpha-1 antitrypsin, prevents digestion of the alveolar walls by elastase. Scientists have reproduced an experimental model of emphysema by instilling elastase into animal lungs. To date, no method of reversing the destruction has been found. Production of synthetic alpha-1 antitrypsin using recombinant DNA technology may ultimately lead to clinical trials of this substance with the intent of halting the progression of emphysema.



Normal honeycomb appearance of alveolar tissue, above, compared with emphysematous tissue showing absence of septae, *below*.

Sickle Cell Disease

Oxygen in the air we breathe ultimately passes into the blood in the capillaries that surround the lung tissue. Although some of it remains dissolved in the plasma, most of it is chemically bound to hemoglobin, a protein in red blood cells (RBC's). Normally biconcave, flexible, and smooth, the erythrocytes carrying oxygen-rich hemoglobin slide in single file through the capillaries that serve all the tissues of the body.

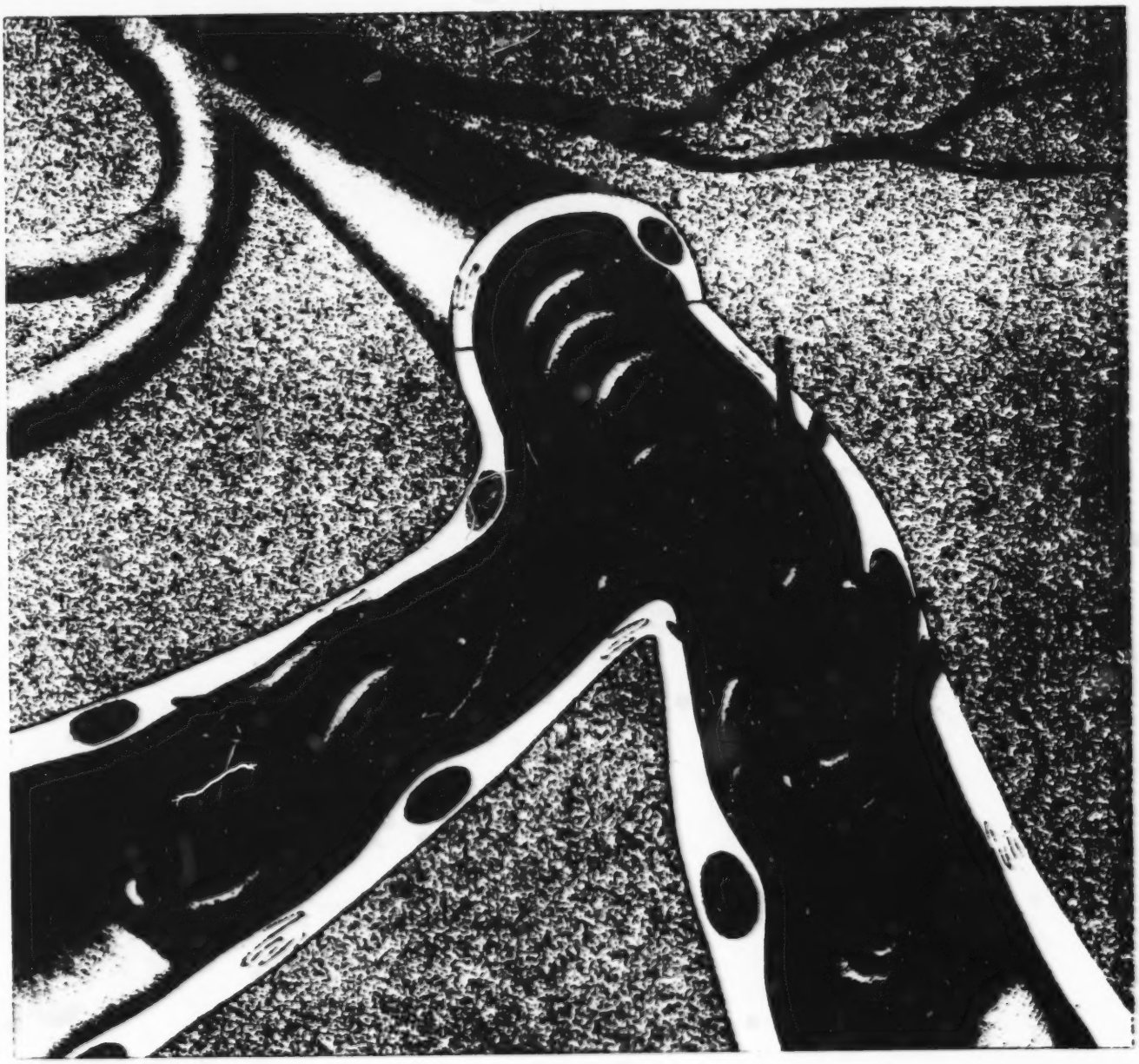
Hemoglobin, the protein that carries oxygen to tissues throughout the body, is composed of two pairs of amino acid chains. In sickle cell anemia, the hemoglobin molecule is altered by the substitution of the amino acid valine for glutamic acid at position 6 of the beta hemoglobin chain. When red blood cells containing this abnormal sickle hemoglobin lose their oxygen to the tissue cells, the sickle hemoglobin can aggregate, form fibers within the red cell, and distort the cell into the characteristic "sickled" shape.

These misshapen erythrocytes are rigid and clog the capillaries, resulting in partial or complete blockage of the blood supply. Although any tissue or organ can be affected by impaired circulation, the heart, lungs, kidneys, spleen, hips, and brain are the most frequently damaged.

The most common clinical manifestation of sickle cell disease is the occurrence of crises—episodes of debilitating pain that can last several days. Organ function gradually deteriorates as a result of circulatory obstruction. In addition, the lifespan of a sickled red cell is shortened from the normal 120 days to approximately 20 days, resulting in a chronic anemia. Individuals with sickle cell disease are also at increased risk for life-threatening infections. This is especially true in infants and children with sickle cell anemia in whom pneumococcal septicemia is the single greatest contributor to mortality through the age of 5.

Sickle cell disease, which affects approximately 50,000 Americans, mostly of African descent, is a hereditary disorder that must be present in both parents to appear in the offspring. The disease lasts a lifetime and exacts a heavy financial and psychological toll on the patient and the family. Modern molecular biology and genetic engineering techniques may ultimately make it possible to repair or replace the defective gene that directs the production of abnormal hemoglobin.

36



Capillaries showing normal and sickled RBC's with sickled cells blocking a capillary.

Perhaps nowhere more than for heart, lung, and blood vessel diseases is technology doing so much to advance medical capability.

The advances have come swiftly and include such diagnostic and research tools as digital subtraction angiography, ultrasound B, magnetic resonance scanning, and cine CT. Among the assist techniques are devices for better arrhythmia control, pacemakers able to slow as well as speed abnormal heartbeats, and left ventricular assist devices (LVAD's).

These new techniques allow speedier, more accurate, and more convenient diagnosis and more effective treatment; they have preventive value as well.

Digital Subtraction Angiography: The equipment.

Sensing What's There

Diagnostic Technologies

Subtracting to See

Digital Subtraction Angiography

A patient is experiencing intermittent weakness and speaking difficulty. To investigate the possibility of an impending stroke, the physician orders digital subtraction angiography (DSA), an outpatient examination of the carotid arteries in the neck that provide blood to the brain.

A fluoroscopic image of the carotids is made and stored in a computer memory; then a dye that is opaque to x-rays is injected through a vein and a second image of the carotids is registered. Comparing the two pictures, the computer produces a "subtraction" image—everything common to the first two images is canceled out. After bones and soft tissue are subtracted, what's left is what's wanted: a picture of the dye in the carotids, which shows whether they are open, narrowed, or ulcerated with the potential of causing a stroke.

DSA is showing promise in evaluating other major blood vessels, such as the aorta, leg arteries, and kidney arteries. It is accomplished in as little as an hour with little patient discomfort. And there is reason to believe that, with further refinement, it may provide relatively quick evaluation of the coronary arteries and intracranial vessels.

Digital Subtraction Angiography: The results. A computer-enhanced color image of heart vessels.

39

Physician uses ultrasound imaging to examine a fetus for congenital heart defects.

Ultrasound B-Scan Imaging

Until 1982, pediatric cardiologists could not see their patients while still *in utero*. They knew that 1 in 500 babies would have a congenital heart defect, but that was only a statistic; there was no way of knowing which baby would be the one.

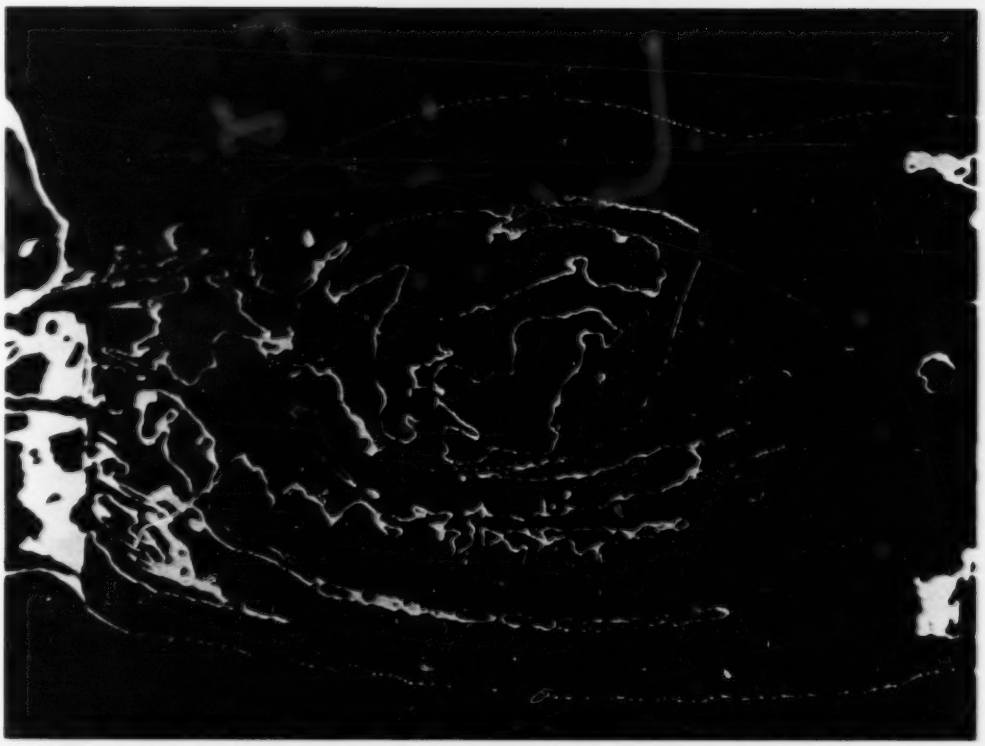
Today, using sophisticated sound wave techniques known as ultrasound B-scan imaging, they can see how the fetal heart has formed and is functioning; discerning details as small as 1.5 millimeters, they can monitor blood flowing through matchstick-size vessels. If a heart problem is found, hazards for the baby may be reduced by modifying care given the mother, and preparations can be made for corrective action soon after birth.

The noninvasive machine sends high frequency sound waves into the body from an external transducer, then analyzes the reflections to produce bright two-dimensional images. A recent NIH consensus conference concluded that ultrasound should not be used for routine fetal monitoring. Because of both its simplicity and ability to pick up as little as a 0.2 millimeter change in vessel wall thickness, however, ultrasound B is a valuable tool for specific fetal diagnostic needs.

Ultrasound B also has applications for adults. In a recent study, for example, 125 men were examined. None had symptoms of stroke, but all were at risk for carotid artery plaques because of high cholesterol levels. Ultrasound B-scan imaging clearly showed plaques in 70. Identifying high-risk adults by such screening techniques alerts them and their doctors to the necessity for preventive health practices to avert stroke.

40

A computer-enhanced ultrasound image of a heart ventricle.



A computer-enhanced magnetic resonance scanner image of the heart.

With Resonance, No Radiation

Magnetic Resonance Scanning

It requires no radiation, no injection. Magnetic resonance scanning shows the insides of blood vessels as if they were empty, pinpointing early, tiny fat deposits on the walls. It can measure brain blood flow to identify stroke risk, image hematomas and blood vessel abnormalities in the head, and determine the extent of tissue damage in heart attack victims. Magnetic resonance scanning also has potential for the noninvasive measurement of the distribution of lung water, pulmonary blood flow, and energy metabolism of the lung.

The basic tool of magnetic resonance scanning is a huge doughnut-shaped electromagnet. When it is turned on, the nuclei of certain atoms in the body—hydrogen, phosphorus, and others—line themselves up with the magnet's field. The magnetic resonance scanning machine then emits a radio pulse that produces another field at right angles to the first, and the nuclei turn to the second field. When the pulse is turned off, the nuclei flip back to original position, sending out their own radio waves, which are detected by a receiver and create a computer-generated image that provides both structural and functional information.

Scanning the Entire Heart

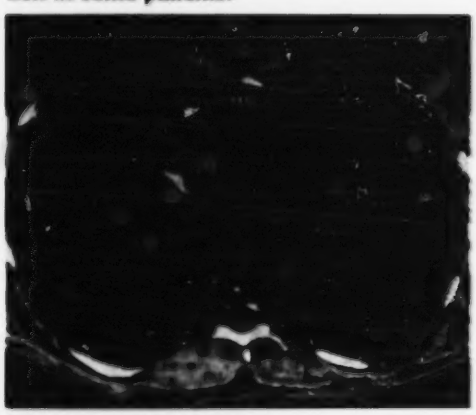
Cine CT Tomography

Late in 1983, investigators at the University of California, San Francisco (UCSF), reported on a revolutionary electron beam scanner able to image the beating heart in three dimensions and measure myocardial (heart muscle) blood flow directly.

The cine CT tomography scanner can take 24 images per second as compared with the one picture every 1 to 5 seconds of conventional whole-body CT scanners. Because it can take exposures at eight anatomical levels, the entire heart can be scanned in "real time" as it actually beats.

Furthermore, reported the investigators, the technique "provides a remarkable display of the cardiac walls, hence thinning and thickening of the myocardium may be measured. Physicians, therefore, may be able to detect coronary artery narrowing earlier and with more precision than is possible at present."

Cine CT, with its cross-sectional "movies," can be used as an outpatient procedure and may reduce the need for cardiac catheterization in some patients.



Cine CT image at the level of cardiac chambers demonstrates mitral valve (MV), aortic valve (AV), major coronary arteries (CX, LAD, RCA) and moderator band (MB).

Detecting Deep Vein Thrombosis

Impedance Plethysmography

The formation of a clot or thrombus in a vein deep in the leg is a potentially life-threatening event. Should the clot become dislodged and travel to the lung, a pulmonary embolism can occur. Diagnosis of deep vein thrombosis (DVT) has been difficult and many times inaccurate, leading to unnecessary treatment with heparin.

A new technique, impedance plethysmography, has been developed that makes diagnosis of DVT in the thigh easier and more accurate. Using cuffs similar to the familiar blood pressure measuring apparatus, the blood pressure in the vein above and below the location of the suspected clot is measured for 5 successive days. The measurements reflecting venous blood flow are charted on graphs representing each examination. If analysis of the results suggests the presence of a clot, x-ray visualization of the vein is indicated to confirm its presence after which heparin is prescribed for the patient to limit extension of the existing clot and prevent formation of new ones. In some cases, the use of thrombolytic agents to dissolve the clot also may be indicated.

X-ray of right and left legs, with impedance plethysmography graphs for each. The bottom graph's straight line indicates an occluded artery in the right leg. The top graph shows the left leg, which has normal circulation.

Computer-enhanced fiberoptic bronchoscope image of the bronchi.

Viewing Distant Lung Tissue

Flexible Fiberoptic Bronchoscopy

The evolution of the science of fiberoptics has made possible the development of sophisticated equipment that permits visualization of areas of the body that heretofore were inaccessible without surgery. Fiberoptics is the technique of transmitting light and optical images along flexible coated glass or plastic fibers. Fiberoptic bronchoscopy makes use of a curving, flexible tube containing these fibers, which is passed into the bronchial tree as far as distal portions of the lung. The unique optical capability of the instrument as well as its flexibility permit direct visual examination of the entire respiratory system.

Since its introduction, the flexible fiberoptic bronchoscope has become an important tool in the diagnosis and management of various lung and airway disorders. Tissues suspicious of malignancy can be biopsied by several methods, the rate of microciliary clearance can be measured, and, with the use of lavage, samples of material from peripheral airways or alveoli can be collected for examination. Fiberoptic bronchoscopy also provides a means of visualizing pulmonary embolism and occult tumors.

Combining laser technology with fiberoptics holds promise for the therapy and detection of lung tumors.

Assist Devices

The Machine That Opened the Heart Surgery Frontier

The Heart-Lung Machine

Until the heart-lung machine became available, the heart had remained the last frontier for surgery because of the problem of trying to operate on the beating pump without disrupting circulation to vital organs. With the machine (also known as the pump oxygenator) taking over the heart's pumping work and the lungs' oxygenating tasks, intricate repairs—coronary artery bypasses and correction of serious congenital defects within the heart—became feasible.

Blood returning from the patient's body through the two great veins, the venae cavae, is introduced through tubing into the machine. In its artificial lung section, oxygen is added and carbon dioxide is removed. The blood is then pumped into the patient's arterial system.

With the machine in operation, the heart can be opened, its beating stopped, and repairs made in a bloodless and motionless field.

The heart-lung machine makes open heart surgery possible.

Support for the Circulation

The LVAD's

Until recently, the only substitute for the heart's pumping action was the heart-lung machine. Modern medical engineering has now developed compact new left ventricular assist devices—blood pumps—that can provide months of continuous circulatory support in animals. If further testing proves them reliable, LVAD's have potential importance for patients with acute left ventricular failure (shock) due to heart attack and have been used successfully in patients with failure after open heart surgery, who would be otherwise unable to be separated from the heart-lung machine.

The temporary LVAD—attached externally to the chest and connected to the heart by short tubes—transfers blood from the left ventricle to the aorta and reduces ventricular work by 90 percent and the heart muscle's oxygen needs by 40 percent. It can give the ailing ventricle a chance to heal and resume functioning, sometimes within as short a period as 48 to 72 hours.

Implantable LVAD's designed for multiyear use are currently being tested in animals, with human clinical trials to come. They could benefit many thousands of patients with end-stage left ventricular failure and congestive heart disease, who are too old for a transplant and not responding to maximum medical therapy.

An experimental left ventricular assist device, implanted.

45

Lifesavers
Advances in Medical Treatment

For patients who already have heart, lung, or blood diseases, no medical advance is more important than new treatment. A patient who has a heart attack in 1984 may be saved by treatments that did not exist 15 years ago. People with asthma who would have faced severe restrictions on everyday activities in the 1960's today can live far more normal lives. Blood resources for transfusion and therapy, once highly perishable and subject to infection, are rapidly becoming safe and more accessible; the list goes on.

What are these new treatments? In many cases, they are new medications and biological products or new uses for existing agents. They also may be new technologies, such as the cardiac intensive care unit, or techniques, such as cardiopulmonary resuscitation. The following are highlights of major advances that occurred in the past decade, just a sampling of the many new lifesavers.

New Treatments for Angina

In the mid-1960's, a German pharmacologist, Professor Andreas Fleckenstein, was working with a new drug proposed for treatment of patients with coronary artery disease. The drug was thought to be another form of beta-blocker, a type of drug that blocks the effect of the natural chemical messenger adrenaline on the heart. But Professor Fleckenstein found that the new drug did not behave quite like a beta-blocker. Upon further investigation, he found that it actually inhibited the flow of calcium ions into and out of the cells of the heart and blood vessels. The drug, which we now know as verapamil, he called a calcium flux blocker. Thus was born the important new class of compounds known as calcium antagonists.

Calcium antagonists are one of the major advances in treating angina in the past decade. Three of these have been approved for use in the United States. Two other major improvements have occurred for angina patients. We now know that the simple aspirin tablet reduces the risk of subsequent death for patients who have had an episode of unstable angina. We also have a better way of delivering the nitrates, a standby drug for angina.

Angina was first noted, and named, by the British physician William Heberden in 1768. He described the chest pain of angina as "a painful and most disagreeable sensation in the breast which seems as if it would take their life away if it were to increase or to continue." Heberden noted that angina often comes on with exercise or strong emotion.

It was some time before clinical investigators found that angina is caused by an insufficient supply of blood, and therefore oxygen, to the heart muscle. When pharmacologists in this century found that the heart is heavily influenced by the chemical messenger epinephrine, they set about making chemicals that would block the effect of this compound. There are two types of sites at which epinephrine, or adrenaline, acts; the one in the heart is called the beta-receptor. These drugs were thus dubbed beta-adrenergic receptor blocking agents, or simply beta-blockers.

But beta-blockers do not solve all problems. They cannot be used for patients who have conditions aggravated by beta-blockade, such as those with asthma or other lung diseases. Beta-blockers may cause undesirable side-effects, such as fatigue, depression, and impotence; and they do not help all patients.

Thus, the advent of calcium antagonists

An NHLBI study showed that patients with angina could exercise significantly longer when they were given both a calcium antagonist and a beta-blocker than with either drug alone.

47

was hailed by many physicians as a significant addition to nitrates and beta-blockers for treatment of angina, especially since calcium antagonists are effective with some patients not helped by beta-blockers.

Calcium antagonists also provide additional symptom relief in patients whose chest pain is only partly alleviated by beta-blockers. For instance, in one study conducted at the National Heart, Lung, and Blood Institute, patients exercised significantly longer on a bicycle when they were given both the calcium antagonist verapamil and the beta-blocker propranolol than with either drug alone. And only two patients had to stop exercising because of chest pain when taking both drugs, as compared to nine patients on single-drug therapy.

Calcium antagonists are especially effective for a kind of angina called angina at rest, which is not provoked by exercise. Beta-blockers are not very effective for this condition.

Calcium antagonists act by a completely different mechanism than either beta-blockers or nitrates. Some calcium antagonists inhibit the flow of calcium ions into cells. Others block the movement of calcium ions within cells. Calcium ions are essential for the contraction of the heart muscle and of the muscles in the walls of the arteries. Thus, calcium antagonists reduce the strength of the heart's contraction and induce relaxation of the arteries. As the heart's workload is reduced, angina also is reduced.

While aspirin is not a new drug, its application to angina is a recent development. The effect of aspirin on unstable angina was established in a study conducted at the Veterans Administration hospitals. During a 12-week trial period, more than 600 men who had just experienced unstable angina took the equivalent of one aspirin tablet each day. Analysis of results showed that those men had only half as many heart attacks or deaths as a comparison group who took an inert preparation.

These findings are welcome because unstable angina has a high risk of heart attack and death. During the 3 months of this study, 10 percent of the group not taking aspirin had a heart attack and 1 of every 30 men died. Aspirin is the first therapy shown to reduce these consequences.

Nitrates have been a standby of angina treatment for many years. Taken regularly, these medications prevent or reduce chest pains in many angina sufferers. However, many people sometimes forget to take their medication. In addition, some people have such severe disease that they have had to take many nitrate tablets each day to control their pain.

These problems are largely solved by a new form of nitrates, a controlled-release system that provides therapeutic blood levels of the chemical for many hours. The controlled-release nitrate comes impregnated in a patch that the angina sufferer places on the chest. By learning how large a patch he or she needs to prevent symptoms, patients can be free of angina without the inconvenience of having to take medication continuously.

Reducing Heart Attack Damage With Beta-Blockers

In 1981 and 1982, the international medical community obtained the answer to a crucial question that had tantalized them for almost 20 years: Can the administration of beta-blockers to patients who have just survived

48

a heart attack prevent some of those patients from dying or having another heart attack? The answer was yes; and it was a resounding yes. Three large trials performed in three different countries with three different beta-blockers all showed that the drugs reduced death by about one-quarter within the year or two following the heart attack.

In the United States, the National Heart, Lung, and Blood Institute organized a trial involving almost 4,000 heart attack patients, half given the beta-blocker propranolol and half given a placebo. A similar trial in Norway enrolled 2,000 patients and used the drug timolol. In Sweden, investigators treated 1,400 high-risk patients with the drug metoprolol.

All three of these trials demonstrated significant reductions in death in the patients given the beta-blocker. In addition, drug-treated patients had another major benefit: They had a 15 to 35 percent lower probability of having another nonfatal heart attack. This is a less dramatic advantage than the saving of lives, but even a nonfatal heart attack is costly, both to the patient and to the health care system.

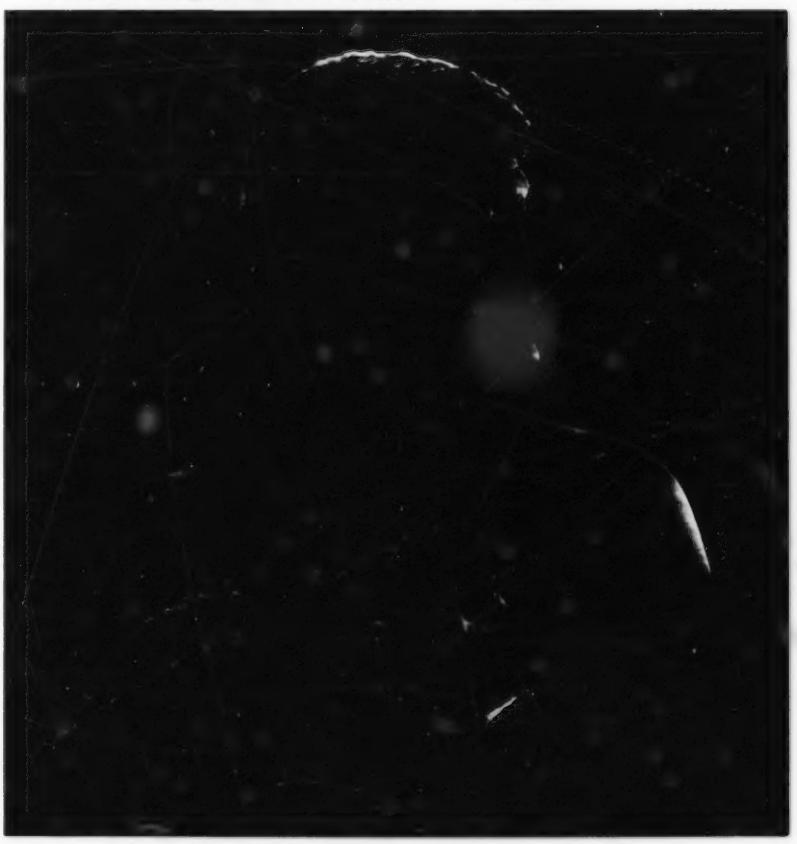
At a workshop held at the NHLBI in May 1982, experts concluded that survivors of recent heart attacks should not be denied beta-blocker therapy unless there are relative or absolute contraindications to beta-blockers. The conferees suggested that clinical studies now in progress may result in continued improvement in the already-impressive clinical results achieved with these drugs.

Alternatives to Digitalis for Heart Failure

The common foxglove, *Digitalis purpurea*, is a two-edged sword. The plant has been used for centuries as therapy for heart failure, a condition in which the left ventricle loses its power to propel blood through the body, with the consequence that fluid backs up in the lungs and the patient has trouble breathing. But eating too much of the foliage is lethal.

When the pharmacological revolution of the early 20th century gave us the active ingredients of the foxglove, the digitalis glycosides, they too, turned out to be dangerous as well as beneficial. A very high dose of digitalis could be toxic. Thus, for a long time doctors using this drug faced a dilemma: The best drug they had for heart failure was of limited benefit to the patients who needed it most.

In the last decade, research on cardiac



By wearing this controlled-release nitrate patch, a patient can be free of angina without following a multidose nitrate medication regimen.

49

physiology has provided improved therapies for heart failure. They consist of alternatives to digitalis for stimulating the failing heart as well as a new class of drugs that reduce the force against which the heart has to pump.

Digitalis acts by strengthening the force of contraction of the heart. Drugs with this effect are called positive inotropes. After decades of digitalis's being the only reliable positive inotropic drug, pharmaceutical science is now providing more potent alternatives. One class inhibits the action of the enzyme phosphodiesterase, which destroys an essential energy component of the contraction mechanism. These new drugs have been called "rather promising, and with an encouraging side-effects profile."

But even the best positive inotropic drug may not be optimal therapy for heart failure, according to Jay N. Cohn, M.D., professor of medicine at the University of Minnesota School of Medicine in Minneapolis. He asks, "Is it therapeutically effective and tolerated to give the patient a chronic stimulus to the contractile force of the heart? Perhaps the decrease in contraction is a defense mechanism." Dr. Cohn has pioneered the clinical use of another, wholly different, kind of drug for heart failure.

These agents reduce the force against which the heart has to work by allowing the blood vessels to relax. They block a protein called angiotensin-converting enzyme, which helps make the chemical angiotensin II. Angiotensin II causes blood vessels to tighten down. Thus, by blocking production of angiotensin II, angiotensin-converting enzyme (ACE) inhibitors greatly reduce blood vessel constriction. Other classes of drugs (e.g., nitrates and hydralazine) also are used for this "afterload reduction."

The first ACE inhibitor, called captopril, came on the market in the United States in 1982. Captopril increases the amount of blood the heart puts out, allows an increase in the patient's ability to exercise, and reduces shortness of breath. Most important, it does this even in patients who are no longer helped by positive inotropic drugs. Because captopril induces relaxation of the arteries, it is also a useful therapy for high blood pressure.

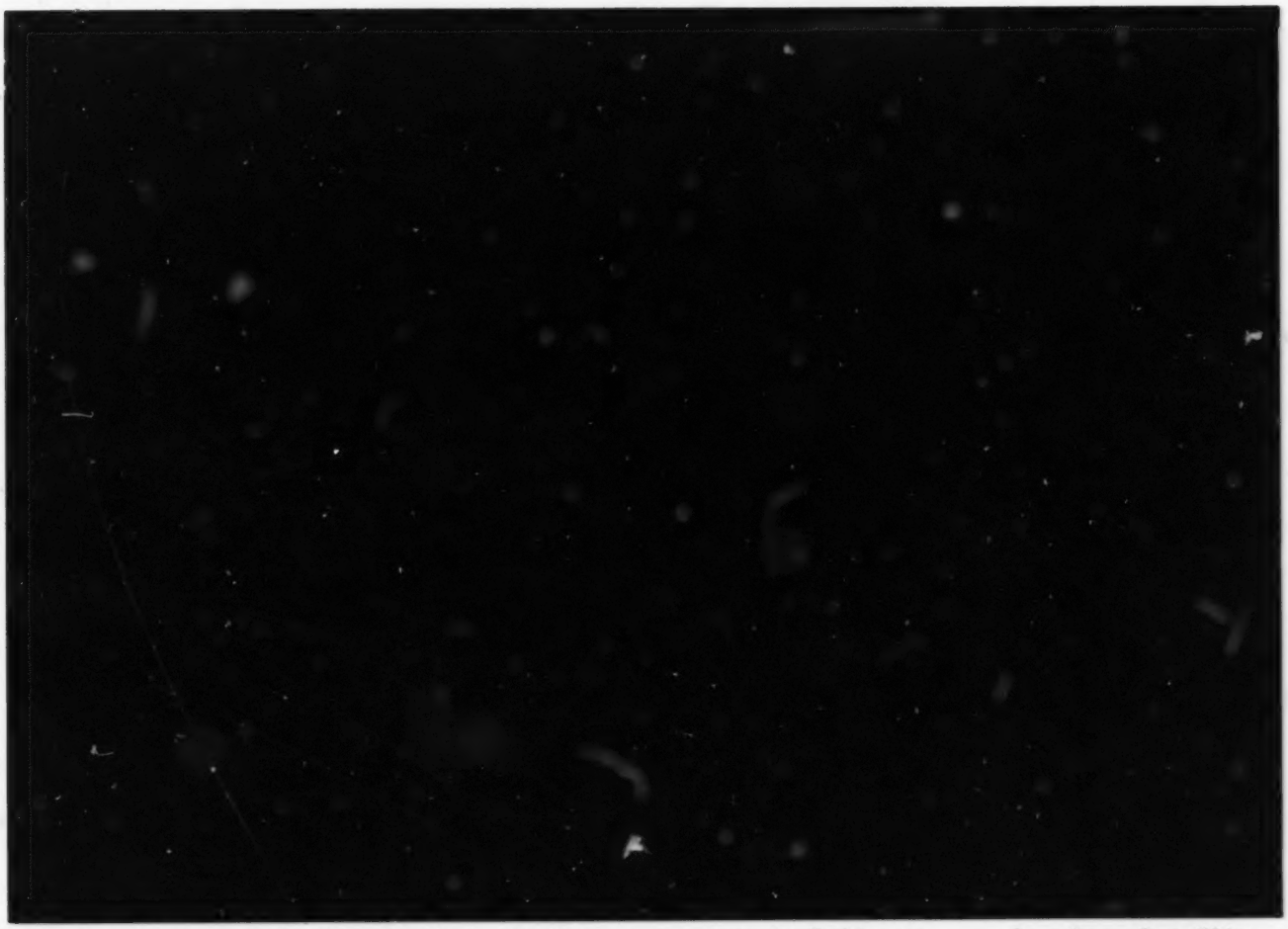
Targeted Therapy for Asthma

They are strong, healthy, young men and women, often competitive athletes. It is hard to believe that they have any physical illness. But once in a while, on an unpredictable basis, while exercising, they will suddenly become short of breath and occasionally even collapse. It was only a few years ago that doctors realized that these people were demonstrating yet another face of asthma, an illness that affects perhaps 9 million Americans, 2 to 3 million of them under the age of 17.

In the last 5 years, laboratory research has led to much improved drug therapy for people with exercise-induced asthma, therapy that is more specifically targeted to the physiological problem that underlies asthma.

Asthma is a condition in which the breathing tubes suddenly narrow and admit very little oxygen, often without any apparent cause. It is thought to be provoked by an immunological stimulus. This idea gained support with the finding that many of the athletes with exercise-induced asthma had attacks regularly following the eating of certain foods such as shrimp and, surprisingly, celery.

The ideal treatment for asthma would be



A new therapy allows athletes who suffer from exercise-induced asthma to work out vigorously, symptom-free.

a compound that relaxes the airways. Such medicines have been available for many years. One of them, theophylline, is a derivative of an herb called ma huang used by the Chinese for 4,000 years to treat asthma.

Unfortunately there are problems with theophylline and the other main drugs used to treat asthma, derivatives of the natural body chemical epinephrine (also called adrenaline). Theophylline has what doctors call a "narrow therapeutic window." This means that the amount that relieves symptoms falls in a very narrow concentration range: just a little less and the patient does not benefit; just a little more and the patient can have very unpleasant side effects such as nausea, stomachache, headache, and dizziness.

The first epinephrine-related drugs relieved asthma symptoms but also affected other systems in the body besides the lungs. For instance, a compound called isoproterenol can cause an uncomfortable speeding up of the heart, restlessness, and headache.

During the last few years, the U.S. Food and Drug Administration has approved several chemically modified forms of epinephrine that have very little effect on any organ other than the lungs. (These drugs are called sympathomimetic compounds, or beta-agonists.) The newer beta-agonists arose from research showing that epinephrine and its relatives act on tiny components on the ends of nerves called receptors. Scientists found that these receptors come in three varieties, and that the three kinds are different in subtle ways. Chemical trial-and-error produced several compounds that affect only the kind of receptors found in the lung.

51

These compounds, called terbutaline, albuterol, and metaproterenol, when taken regularly, effectively prevent most asthma attacks. Now athletes and others with exercise-induced asthma can take a few puffs of terbutaline or albuterol from an inhaler and work out without fear.

Synthetic Hemoglobin for Improved Oxygen Delivery

In 1966, Dr. Leland Clark of Children's Hospital Research Foundation in Cincinnati submerged mice completely in liquid. The mice did not drown. Rather, they lived and stayed healthy for several weeks. The trick was that Dr. Clark had put the mice into a solution of organic compounds called perfluorocarbons, a kind of synthetic hemoglobin. In 1968, rats whose blood was completely replaced by perfluorocarbons lived a normal lifespan. The same result was achieved with dogs in 1975.

More recently, the use of perfluorocarbons has been refined to the point that they are being used on an investigational basis in humans. The basis for the biological effect of organic compounds is their remarkable ability to carry large amounts of oxygen. Moreover, the bond between perfluorocarbons and oxygen is readily dissociable, so that when these compounds penetrate living tissues they release the oxygen to the cells that need it.

The first use of perfluorocarbons in human patients occurred in the late 1970's. (Prior to use in patients, the material was used to replace portions of the blood of the healthy corporate executives of the company that has developed this material. No adverse consequences occurred.)

So far, in the United States, perfluorocarbons have been mostly used for Jehovah's Witnesses undergoing surgery. Jehovah's Witnesses have a religious restriction against using blood products. In a small clinical trial conducted at the University of California, Los Angeles, Medical Center, doctors found that one form of perfluorocarbons increased the margin of safety for the patients' surgical procedures and caused no adverse effects.

Besides the use in those with religious objections to receiving blood, perfluorocarbons are being tested to deliver oxygen to the brains of those who have suffered strokes. Because perfluorocarbon particles are much smaller than a red blood cell, they can penetrate into narrow capillaries in the brain. They could also be used during natural disasters and war, when blood is in short supply.

The chief drawback of current perfluorocarbon preparations is that they must be administered along with high concentrations of oxygen to be effective. This is not a serious problem in the surgical situation, however.

The Coronary Care Unit

New Technologies Enhance Cardiac Survival

In the late 1950's, it was realized that persons having a heart attack, or myocardial infarction, were at a greatly increased risk of death within the ensuing few hours. Attempts to solve this problem led to what we now know as the coronary care unit, commonly referred to as the CCU.

"Three landmarks in the genesis of the CCU occurred in the early 1960's," relates Dr. Thomas Killip, chairman of the depart-

52

ment of medicine at Beth Israel Medical Center in New York. The first was the establishment in a community hospital in Kansas City by Dr. Hugh Day of a single room in which all MI patients were placed for the first few days while their heart rhythm was continuously monitored. Specially trained nurses staffed the room. "This was the first CCU," says Dr. Killip.

The second was the report by a Toronto physician that many MI patients spontaneously developed ventricular fibrillation (VF), a lethal disturbance of heart rhythm. A Philadelphia physician subsequently trained nurses to read electrocardiograms (EKG's) and defibrillate patients.

The third step, according to Dr. Killip, was the demonstration by a group at Johns Hopkins University Hospital that a new resuscitation technique could keep MI victims alive without opening the chest. "At about the same time, someone pointed out that lidocaine was effective against ventricular arrhythmias and remarkably nontoxic."

Thus, the three basic therapies of the CCU—defibrillation, resuscitation, and antiarrhythmics—were in place.

Debate followed on whether this expensive and technologically intensive innovation actually saved lives. "My own view is that CCU's do indeed make a difference," says Dr. Killip, "but mostly for a subgroup of the patients who get to the hospital within 72 hours of the MI."

Substantial evidence supports the efficacy of arrhythmia prophylaxis, cardiac monitoring, and resuscitative capabilities in lowering mortality, especially in the first 6 to 12 hours after infarction. Current standards of American medical practice include admission to a coronary care unit for patients with definite acute myocardial infarction.

"The next step, which occurred during the 1970's, was to move into measuring cardiac physiology, particularly with the Swan-Ganz catheter," Dr. Killip says. The Swan-Ganz catheter directly measures the condition in both ventricles of the heart. It is floated into the right heart through the venous circulation, where the right ventricle is monitored. Then it is advanced into the pulmonary artery, where a balloon on its tip is inflated and the so-called wedge pressure is obtained. This measures the pressure under which the left ventricle is being filled.

"Basically the Swan-Ganz catheter tells you whether people are in cardiac shock (very low blood pressure) or unremitting heart failure." If the filling pressure of the left ventricle is low, then the effective treatment is to give fluids to combat dehydration. Patients with normal filling pressure have pump failure, which is the inability of the left ventricle to move enough blood around the body.

Even patients with heart failure are benefiting from the use of the Swan-Ganz catheter in the CCU. "The current greatest contribution of the catheter to the treatment of heart failure is that we can directly evaluate in individual patients whether a drug is doing any good," Dr. Killip says.

Finally, he points out one unmeasurable but significant contribution of the CCU. "The CCU ethic now permeates medicine. Lessons from the CCU are being applied to all heart attack victims, both in the hospital and in the community. CCU philosophy has become state of the art."

CPR
Reviving the Heart After Cardiac Arrest

One of the most successful means of preventing cardiac deaths has been the advent of cardiopulmonary resuscitation (CPR). CPR is a technique for restoring breathing and heartbeat by applying manual pressure to the patient's chest and breathing into his or her mouth. It can be used by medical specialists or laymen to keep patients alive until they can reach sophisticated life support equipment. Because of its demonstrated effectiveness, many communities have developed programs to train laymen in the technique. One such program in Seattle, Washington, began in 1971 as an outgrowth of intensive training of paramedical personnel in Seattle, a project called Medic-1.

Leonard A. Cobb, M.D., now chairman of medicine at Harborview Medical Center in Seattle and professor of medicine at the University of Washington, explains the rationale behind community CPR. "Given that patients have cardiac arrest outside the hospital, there are two important determinants of survival. The first is how rapidly CPR is administered. The second is how rapidly advanced cardiac life support is provided. We realized that we could meet the first requirement by training public bystanders in CPR. But, Dr. Cobb points out, "CPR training of the public would not have been very useful unless we had a first-class emergency response unit."

It was the existence of Medic-1, in fact, that made possible the community-based resuscitation effort, called Medic-2, according to Dr. Cobb. "What made Medic-2 work was that it was an offshoot of the successful fire department program and people were familiar with it, that it was run by the fire department, and that it had lots of downtown civic support, such as from the Rotary."

Dr. Cobb and his colleagues have studied the results of Medic-2 intensively. They have demonstrated that bystander CPR has an impressive benefit. For instance, about one-third of all persons with cardiac arrest in that year were given CPR by a trained layman. Those persons were discharged home from the hospital 43 percent of the time, compared to only 21 percent of the people not given bystander CPR. (The low rate of non-CPR patients is in spite of a 3-minute response time for emergency units in Seattle.) The hospital mortality was 54 percent among cardiac arrest victims not helped by a bystander, but only 25 percent among those given bystander CPR.

The Seattle figures show that no medical background is needed to be able to give effective CPR. Of those cardiac arrest victims given CPR by a bystander with a medical background, 42 percent were discharged home. The comparable figure for persons with no medical background was 53 percent. Once the efficacy of Medic-2 was demonstrated, community CPR was advocated by the American Heart Association in 1974 and by the American National Red Cross shortly thereafter. Both of these organizations offer training programs to teach the lay public how to perform the technique.

Currently about 40 percent of the people in the city of Seattle have been trained in CPR. But Dr. Cobb points out that sheer numbers aren't enough. "About 70 percent of cardiac arrests occur in the home," he notes. "Thus it is particularly important for middle-aged and older women to learn CPR, because they are the ones who might be living with a man who is at high risk of cardiac arrest."

54

Programs sponsored by groups such as the American Red Cross and the American Heart Association train men and women in the community to perform CPR.

55

Improving the Outlook for Children

As every parent knows, medical advances seem especially critical when the patient is a child. Congenital and hereditary heart, lung, and blood diseases can have devastating, sometimes fatal, effects for the thousands of children who are born with them. Improving the outlook for these children is an important objective for basic and clinical researchers, who are looking to fields as diverse as immunology, genetics, nutrition, surgery, and medical technology for the cures to these diseases and disorders. For children with congenital heart defects, cystic fibrosis, and hemophilia, some of the answers have already been found, dramatically improving their prognosis.

Correcting Congenital Defects

Each year, 25,000 babies are born in the United States with heart and vascular malformations—8 in every 1,000 live births. The errors occur unpredictably, their causes still unknown. Some may stem from untoward internal events during pregnancy such as endocrine disturbances or perhaps mild infections; there may be, additionally or alternatively, environmental influences such as maternal use of alcohol. (A few studies have demonstrated seasonal and geographical clusters.) They are not hereditary as is the case with some other congenital conditions.

At one time, such babies died within days, weeks, or months. Now, an increasing majority survive, thanks to modern surgery.

Transposition of the great arteries, the two major byways bearing blood away from the heart, is a common congenital defect. In a child with this malformation, the aorta, the normal route of freshly oxygenated blood from the left side of the heart, recirculates oxygen-depleted blood laden with waste products while the pulmonary artery uselessly recycles blood through the lungs. The result is massive oxygen starvation throughout all the body's organs and cells, including the heart itself.

Similarly causing oxygen deprivation is the anatomic anomaly known as the tetralogy of Fallot (for the French physician who first described it), which consists of a narrowed pulmonary artery, concomitant enlargement of the right ventricle, displacement of the aorta, and an opening between the heart's lower chambers. Other congenital cardiac malformations include patent ductus arteriosus, in which a fetal duct between the pulmonary artery and the descending aorta, normally closed before birth, has remained open; ventricular septal defects, malformations in the wall between the lower chambers; and coarctation (narrowing) of the aorta.

Occasionally, some of the malformations right themselves spontaneously or are too small to be important; this is sometimes true of septal defects. But in most cases, corrective surgery will be needed. By the 1970's, procedures had been developed to correct most congenital cardiovascular malformations. Yet obstacles remained, relating chiefly to the small size of the patients. Diagnosis was difficult, as was restructuring such small organs and vessels. Major advances over the past decade have changed this picture dramatically.

While x-rays and electrocardiograms provide physicians with certain information, recently developed noninvasive technologies such as echocardiography and nuclear imaging are major factors in increasing diagnostic accuracy. (Precise diagnosis still requires such delicate invasive procedures as

At one time, babies with particular congenital heart defects died shortly after birth. Today many of them survive as a result of surgical advances.

Therapy—and life expectancy—for children with cystic fibrosis has improved significantly over the past two decades.

cardiac catheterization and angiography.) The refinement of microsurgical techniques has revolutionized and broadened the scope of corrective procedures, permitting successful repairs even in newborns. The heart-lung machine, which first made open heart surgery possible in the 1950's, is now combined with deep hypothermia. This temporary cooling to temperatures as low as 20° C (68° F) makes state-of-the-art reconstruction in a virtually bloodless arena possible.

But the proverbial ounce of prevention is still preferable to many pounds of technologically sophisticated cure. Even surgical success does not necessarily assure the sort of life that can be called optimal; residual problems, necessitating lifelong restrictions in activity, may still persist and diminish the quality of life for nearly one-third of those who survive. Thus, the challenge now is to find the reasons for the malformations—to find out how, when, and why they happen—so that the precipitating events might be averted and fewer newborns will need to face major surgery during their first days of life.

An Improved Prognosis in Cystic Fibrosis

According to actuarial tables, a child born in the United States this year enjoys a life expectancy of 75 years. But if that child's parents happen to be 2 of the 10 million Americans (1 in every 20) whose cells contain the cystic fibrosis (CF) gene—even though they are not ill themselves—and the child has received one from each parent (the odds are 1 in 4), that infant is statistically unlikely to live long enough to graduate from college.

Two such genes combine to produce cystic fibrosis in 1 of every 2,000 white babies born in our Nation each year (the rate is substantially lower in blacks, about 1 in 17,000). While there are 12,000 to 13,000 patients currently registered with the National Cystic Fibrosis Foundation, there are believed to be about 30,000 with the disease, and the number may well rise in the future.

CF was not recognized as a distinct disease until the late 1930's, when certain combinations of symptoms began to be noticed. By the early 1950's, other features had been documented, and CF is now viewed as a systemic disorder that may affect a number of parts of the body, although its manifesta-

55 D

tions and severity may vary from one affected individual to another.

A salient characteristic of CF is abnormally thick and viscous mucus, which obstructs a number of the body's tracts, notably the airways, with a high susceptibility to lung infections, and the pancreatic ducts, preventing normal digestion and leading to malabsorption and malnutrition. The sweat of CF victims contains abnormal salt levels, which can cause critical heat intolerance in severe cases. (Sweat testing has become an important factor in confirming the diagnosis.) The respiratory malfunction can lead to complete debilitation and may also open the door to complications such as cor pulmonale, a heart disease caused by pulmonary hypertension, which can develop as a result of chronic lung dysfunction.

Therapy, however, has improved significantly over the past two decades. An increase in the number of effective antibiotics has meant better treatment for infection. Such diagnostic strides as echocardiography, improved pulmonary function testing, and nuclear imaging have meant more accurate assessment of patient status. Better understanding of nutritional needs and ways of meeting them have sustained youngsters who might otherwise succumb to acute malnutrition. And the prognosis has improved as well. The 20-year life expectancy cited earlier represents a marked increase over the under-10-years figure of the mid-1960's. In fact, that statistical median is exceeded in many cases, and there are now CF patients in their twenties and thirties. It is now recognized, too, that in some milder cases, there are no childhood difficulties at all, and CF is not diagnosed until adulthood.

Many pressing challenges still face researchers, mostly at a basic level. If CF is to be prevented or cured, it must first be far better understood and its biochemical nature defined and delineated. Such questions as its underlying mechanism need to be answered. It has been established that CF patients' immune systems per se are intact. Thus, localized defense mechanisms of the lung must be explored, with an eye to enhancing them and staving off the ever-present threat of critical infection. A reason for the range of CF manifestations from mild to severe must be found. Scientists are also working to find genetic markers for CF. A number of substances have been identified that are associated with the CF process. Researchers hope to be able to link specific cell components to the CF gene, which could allow identification of carriers and prenatal diagnosis of the condition.

How Cystic Fibrosis Is Inherited

CF is a recessive disorder: the gene is "counteracted" by unaffected inheritance—that is, absence of the CF gene—from the other parent, and a child can be afflicted only if the gene is passed on by both parents. A child receiving the gene from just one parent is a healthy person but a carrier, who can relay it to his or her own children. The following shows the odds of producing offspring who have the disease or are carriers of it. These odds remain the same with each child, just as the outcome of a coin toss is uninfluenced by prior tosses.

	Probability of		
Parents	Unaffected Child	Carrier	Child With CF
Unaffected + carrier	50%	50%	—
Both carriers	25%	50%	25%
Unaffected + CF patient	—	100%	—
Carrier + CF patient	—	50%	50%

55 E

Therapy Now Means a Normal Lifespan

Hemophilia. The word literally translates as "love of blood," but the emotion it evokes is fear. It was Queen Victoria's heritage to three of her children: Through her son Leopold, a victim, and her daughter Beatrice, it descended through the generations of Spanish royalty. Through her daughter Alice and Alice's daughters Alexandra and Irene, it was relayed to the ruling houses of Germany and Czarist Russia. (England's Queen Elizabeth II escaped, because her great-grandfather Edward VII, another of Victoria's sons, was unaffected.) Today, in our own Nation, there are an estimated 15,000 to 20,000 patients and an unknown number of carriers of the gene. The disease is almost invariably passed from mother to son; a daughter may become a carrier from either parent. (See accompanying chart.)

In a sense, today's victim of hemophilia is fortunate—at least as compared with those of a generation ago. Hemophilia's main threat is popularly supposed to be the possibility of bleeding to death from the slightest scratch. That danger, however, is and has always been small. It is true that surgery or major injury holds that potential, but hemophilia patients are no more liable to those events than the rest of us. The main danger, because it is unpredictable, is that of internal hemorrhage—sometimes following minor bumps or bruises, often occurring spontaneously. Repeated bleeding into joints and muscles is common, causing severe pain. It is temporarily paralyzing, and without treatment, is permanently crippling. Blows to the abdomen, chest wall, neck, or head can lead to injury of internal organs, respiratory failure, or cerebral hemorrhage.

Only in the late 1940's was the specific defect in hemophilia discovered: the lack (or, possibly, inactivity) of one of two plasma proteins essential to the blood-clotting process. For approximately 9 of 10 hemophiliacs, in whom the disorder is known as hemophilia A, this is a substance called factor VIII; in the remainder (hemophilia B or Christmas disease), it is a different protein, known as factor IX.

Through the 1950's and 1960's, the answer to bleeding episodes and the accompaniment to any surgery became transfusions of fresh plasma, which provided the elements needed for blood to clot normally. But there were problems: Severe transfusion reactions were not uncommon, and the additional fluid volume sometimes posed a harrowing choice between additional plasma infusion and an overload that could precipitate fatal congestive heart failure. Treatment of course required hospitalization—sometimes lengthy and invariably expensive.

Later it was discovered that the clotting factors could be extracted from plasma and concentrated, eliminating those fresh-plasma problems. Today, these concentrations are used, and for the less serious, nonlife-threatening bleeding episodes, they are commonly administered at home by a family member or by the patient himself. Today, most hemophiliacs in our country can and do lead near-normal lives, and many can look forward to a normal lifespan.

That improvement is also due in part to government action. Under the Hemophilia Diagnostic and Treatment Center Program, established by Congress in 1975, there are now 25 federally funded regional centers staffed by health care teams experienced in dealing with the continuing problems of the

Thanks to research advances, teenagers with hemophilia today can live a near-normal life, and many can look forward to a normal lifespan.

Hemophilia Inheritance

Hemophilia is an X-linked recessive disorder: the gene is on the X chromosome and can be "counteracted" only by an X chromosome that does not carry the gene. Thus, a male (XY) who receives the gene will necessarily have the disease, and a male cannot be a silent carrier. The possibilities can be shown this way:

Father	Mother	Probability of Carrier, if Daughter	Probability of Hemophilia, if Son	Probability of Hemophilia, if Daughter*
Unaffected	Carrier	50%	50%	—
Hemophilia	Noncarrier	100%	—	—
Hemophilia	Carrier	50%	50%	50%

*A theoretical possibility but rarely reported. Hemophilia does not affect fertility, but many if not most hemophiliacs opt not to have children.

All of a hemophiliac's daughters, who have received one X chromosome from their father, will be carriers, but none of a hemophiliac's sons will receive the gene, because the father has passed on to them only a Y chromosome. There is a 50–50 chance that a carrier will relay the gene to her children of either sex.

There is no accurate test for the carrier state. A blood test, which must be performed when a woman is neither pregnant nor taking oral contraceptives (either can skew the results), *may* show lower-than-normal levels of a key clotting factor, but in 10 to 20 percent of carriers, the levels are normal.

hemophiliac and his family—problems with which an individual physician, who may have only a single hemophiliac patient, would be far less familiar. In addition to primary care physicians, such teams consist of hematologists, orthopedists, physical therapists, psychiatrists and other counselors who can cope with patient and family anxieties, genetic counselors, and specially trained nurses.

The program has been highly successful, reducing patient costs and helping patients to a far more productive and enjoyable life. Average health care costs per hemophilia patient before 1975 could range up to $22,000 a year; by 1982, the figure had fallen to just over $5,000 (largely covered by insurance). In the same period, the average number of days spent away from school or work by hemophiliacs dropped from between 20 to 60, to 8; the average hospital stay dropped from 2 weeks to 2.5 days. And unemployment among adult hemophiliacs fell from 36 percent to 13.6 percent.

As with cystic fibrosis, the number of hemophiliacs now living long enough to reproduce has increased, and they invariably produce daughters who are carriers of the gene; thus, the overall number of carriers and hemophiliacs in subsequent generations may increase as well. A recent study by the National Heart, Lung, and Blood Institute suggests that future demand for factor VIII concentrate could conceivably exceed the Nation's resources, particularly if, as seems possible, there is a trend toward administering it prophylactically (that is, before bleeding episodes).

Concern about inadequate supplies of factor VIII and about the slight risk of transmissions of blood-borne disease by treatment could be eliminated entirely if supplies were not dependent on human donors. That may be possible: the gene for factor VIII has now been found and cloned (see p. 81), and production of synthetic factor VIII has begun. In addition to providing a safer protein and ensuring adequate supplies, factor VIII produced by genetic engineering might also be cheaper. Work on the process continues, and it is hoped that an artificial factor VIII might be ready for clinical testing within the next few years.

Health Education/ Risk Reduction

Helping Healthy Children Stay Healthy

Research has made strides in saving infants and children unlucky enough to have a congenital or hereditary disorder. Most children, however, are born healthy, and researchers have recognized that helping children develop good lifestyle habits while they are young is a good way to help them stay healthy. School health and other educational initiatives are one strategy for making good health practices second nature.

While health promotion efforts are directed to adults, longtime habits such as an imprudent diet, inactivity, and smoking may be more difficult to break than to prevent. Targeting children for risk reduction has another rationale as well: Some may already have risk factors that are the precursors of adult disease.

A screening program of 11- to 14-year-olds in New York City in the late 1970's, for example, found that 1 in 10 smoked cigarettes regularly, a quarter were overweight, 27 percent scored low in cardiac-response exercise testing, and more than one-third had cholesterol levels over 180 mg/dl (levels above 220 mg/dl are considered treatable for adults). Altogether, more than half the youngsters evidenced at least one risk factor for cardiovascular disease. Without intervention, such risks can increase. It was found, for instance, that 45 percent of the U.S. casualties in the Vietnam war—whose average age was 22—already had evidence of atherosclerosis, fatty blockage of the arteries.

One active health education program for children is called "Know Your Body," developed by the American Health Foundation and funded by both the National Heart, Lung, and Blood Institute and the National Cancer Institute. The program is now in a pilot stage in a number of communities across the Nation, with ongoing evaluation of the results at various grade levels. Thus far, it appears that its screening/teaching/behavior modification approach does work and can have significant impact, by promoting not only the acquisition of information but also the alteration of lifestyles.

During an academic year in one Evanston, Illinois, school, for example, the number of children with heart disease risk factors fell from 31 to 17 percent. In the New York area, 51 percent of a group of overweight seventh- and eighth-graders successfully lost weight, as compared to 16 percent of a "control group" who were weighed and told they were overweight but were not offered the program. Similar successes have been scored in comparisons of gains in health knowledge, cessation of smoking (or not starting in the first place), changes in eating habits, and drops in cholesterol levels. Currently, two groups of youngsters are being followed from the fourth grade through the ninth, to see if the positive effects recorded thus far can be maintained. The studies are scheduled for completion in 1985 and 1986.

A variety of other childhood health education-risk reduction programs are also in use across the country. Although long-term studies are needed to document the best strategies, many of the approaches appear promising, particularly in the areas of smoking and high blood pressure.

It will also be helpful, of course, if the importance of good health habits is reinforced by the pediatricians and family physicians who care for our children. To that end, the NHLBI has instituted the Preventive Cardiology Academic Awards Program, which provides funds to U.S. medical schools that have the interest and ability to infuse their curricula with quality instruction in preventive medicine.

School health education programs help children develop good lifestyle habits, such as regular exercise, to help them stay healthy.

Prevention:
Framingham's Legacy

The town of Framingham, Massachusetts, 30 miles southwest of Boston (population 72,000) is only a small dot on the map, but in the atlas of epidemiologic studies, it is the world's capital.

In 1949, every other man and woman ages 30 to 62 in the town agreed to enter the Framingham Heart Study, committing themselves to return periodically for checkups for the rest of their lives. This project, launched by the then-fledgling National Heart Institute, had an ambitious goal: To identify factors contributing to the subsequent development of coronary heart disease and high blood pressure.

When the study began, 5,127 of the 5,209 participants were free of heart disease. "The aim always has been to see what makes people stay healthy as well as what causes them to become ill," reports Dr. William Castelli, the study's medical director.

All but 2 percent of those who entered the study have stayed in it; even those who have moved away loyally keep in touch, coming in for an exam when they visit Framingham. Some 2,500 of the original participants are still alive; the oldest is now 96, the youngest are in their sixties, a stimulus to expand the exploration of the effects of aging. Children of the original participants along with their spouses, some 5,000 persons, entered the "offspring" study 12 years ago to help clarify the role of heredity as well as environment in heart and blood vessel diseases.

The Framingham study's key findings include:

- The higher a person's blood cholesterol, the higher his or her risk of suffering a heart attack, even when cholesterol levels fall within the range presently regarded as "normal," that is below 220 milligrams per deciliter. (Framingham data suggest that the "ideal" level, at which heart disease is unlikely, is under 150 mg/dl.)
- Similarly, the higher one's blood pressure, the higher the risk. Borderline high blood pressure (systolic pressure 140 to 159 mm Hg, diastolic pressure 90 to 94 mm Hg) increases coronary heart disease by 50 percent and leads to a threefold increase in stroke.
- Cigarette smoking nearly doubles the rate of coronary heart disease. The more one smokes, the higher the risk. Filter cigarettes offer no advantages in reducing one's risk of heart disease.
- Regular, vigorous exercise seems to protect against heart disease.
- Obesity contributes to high cholesterol levels and high blood pressure, and seems to make an independent contribution to one's risk.
- Time-conscious, hard-driving, impatient, dissatisfied people have roughly double the risk of heart disease of those who lack such personality traits, particularly if they are otherwise at risk because of high cholesterol, elevated blood pressure, and the like.

Framingham has been the impetus for numerous nationwide clinical studies. These include the Veterans Administration Collaborative Study, which reported in 1967 and 1970 the advantages of controlling blood pressure, and the Multiple Risk Factor Intervention Trial, whose results, reported in 1982, suggest benefits of controlling blood pressure, reducing smoking, and improving diet. Investigations at Framingham prompted researchers to ask whether lowering cholesterol reduces the odds of suffering a heart attack, a question answered in the affirmative by the results of the Lipid Research Clinics Coronary Primary Prevention Trial.

Framingham participants have their periodic checkups in a white frame house that serves as the study's medical facility.

Framingham's former medical director, Dr. William Kannel, counsels study participants about preventing heart disease. "Waiting for . . . disease to appear in coronary candidates . . . can no longer be justified," he says.

"As an epidemiologic study, Framingham suggests associations," observes Keaven Andersen, the study's resident statistician. "Clinical trials demonstrate cause and effect."

"The advantage of Framingham is the reliability of the data," Dr. Castelli says. "As a prospective study, measurements are made years before illness appears."

At times, questions have been raised as to whether Framingham is a "typical" American town. But studies of other populations—business executives in Minneapolis, workers at the Peoples Gas Company and Western Electric in Chicago, longshoremen in Los Angeles, residents of Albany (New York), Tecumseh (Michigan), Evans County (Georgia), Honolulu, and Puerto Rico and others—all have yielded results similar to those of Framingham. Their major lessons also are the same: Reducing fat intake, keeping weight down, controlling blood pressure, avoiding smoking, and exercising regularly can make a difference. The dramatic decline in death from heart disease in the United States over the past two decades suggests that Americans are heeding the prevention message.

"Waiting for symptomatic cardiovascular disease to appear before instituting treatment in coronary candidates is a form of brinkmanship that can no longer be justified," says Dr. William Kannel, former medical director of the Framingham study and now head of the department of preventive medicine and epidemiology at Boston University. A heart attack, he submits, is a "medical failure."

Early detection and the grounds for preventive action are Framingham's legacy. The town was chosen as a possible site for the government's heart study because of both its proximity to Boston's numerous medical centers and expert consultants and its previous participation in an epidemiological survey, during the 1920's. In a project sponsored by the Metropolitan Life Insurance Company, teams of doctors and nurses went from door to door in Framingham, identifying active cases of tuberculosis in an effort to stem the spread of the disease.

In 1949, after statisticians drew a random sample of the town's adults, a committee of community residents volunteered to enlist their neighbors. Most of those invited to participate accepted; husbands and wives also were given the option to join. In those more innocent days of medical research, no consent forms were used.

Participants Richard and Helen, both 72, were 38 when the study began. Richard, who worked at the Dennison Company then as now, one of the town's major employers, trusted the company doctor's support for the study. "I liked the idea of personally contributing to scientific research," he says. Helen's motivation for joining was more pressing: a strong family history of heart disease.

Richard and Helen, study participants who have been sports enthusiasts since childhood. Framingham results have reinforced their active lifestyle.

"I hoped that somewhere down the line the doctors would have something helpful to offer, if not for me, for my children," she recalls.

They return every 2 years to the white frame house that serves as the study's medical facility to give blood and urine for a battery of tests, run on a treadmill, undergo studies of heart function, and breathe into devices that measure their lung capacity and the carbon dioxide in their breath. The exams, designed to cause patients a minimum of discomfort, always include certain basics such as blood pressure measurements, but as technology has become more sophisticated, new tests have been added. Recent additions include echocardiography, which reveals anatomic features of the heart, and phonocardiography, which identifies functional abnormalities, along with tests of vision, hearing, and mental abilities.

The most recent round of tests took 3 hours, and for 24 hours afterwards, the subjects wore a device that automatically recorded their heart rate and blood pressure. Like other volunteers, they are told the results of their tests and, if they wish, may have them sent to their personal physicians.

"Being part of the study hasn't made us live any differently, but it probably has reinforced certain habits we already had," Richard asserts.

The couple has enjoyed lifelong good health. Although Richard developed rheumatoid arthritis and high blood pressure in his sixties, he keeps both under control with daily medication. A tribute to his health is his 43-year record as a volunteer blood donor; he has given over 15 gallons of blood to the Red Cross. Helen worries about her weight—she would like to lose a "few" pounds—but she has no other health concerns.

Both have been sports enthusiasts since childhood, and they play tennis several times a week. Their diet consistently has been the type that doctors today describe as "prudent," high in vegetables and fruits, with meat limited to perhaps three servings a week.

Every 2 years, participants receive a battery of laboratory tests—from blood and urine analyses to echocardiography.

If Richard and Helen are "typical" of heart study participants, so too is John, 66. Like many Americans, he acknowledges with a sigh, " I should exercise more and get my weight down." The owner of a television sales and service center, he leads a sedentary life. For his once-a-week golf game, he rides a cart. He carries about 185 pounds on his 5-foot 9-inch frame.

John credits the heart study staff with discovering 9 years ago that he had high blood pressure, a condition for which he now takes daily medication. But it took a heart attack 4 years ago, followed by several painful attacks of gout, to push him into making dietary changes such as cutting back on salt and alcohol. While he relishes his wife Lena's traditional Italian cooking, he now passes up the chicken livers and other organ foods he once loved, and he trims the fat from meats.

"I'm learning," he says with a grin. "And I'm glad that my four children pay more attention to their health than I ever did."

John's son Paul, 35, who also works in the family business, is 6 feet tall and weighs a solid 210 pounds, the result of years of weightlifting. He works out at a health club for 90 minutes three times a week, although the emphasis, he notes, is on body-building rather than on strength or endurance. Knowing that he has borderline high blood pressure, averaging about 140/90, he has bought an electronic sphygmomanometer to monitor his pressure himself. "Last time, the doctor told me to restrict salt and keep my weight down, which I try to do. I wasn't advised to take any medications, and I would like to avoid medication therapy if I can," he says.

His reason for enrolling in the offspring study is an eminently practical one. "I'm not the type that goes for checkups often. I figure that if there's something wrong, the doctors there will find it soon enough."

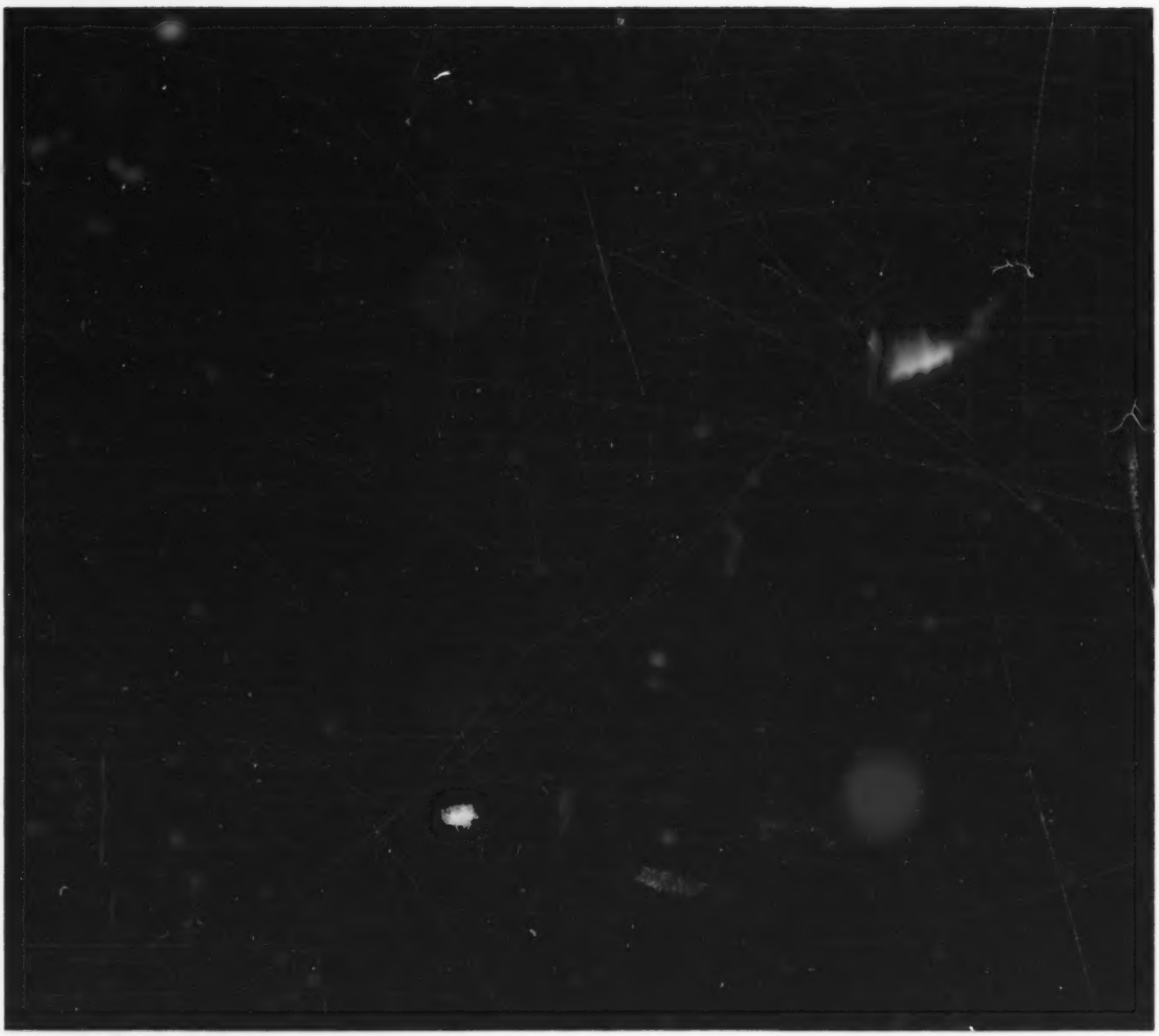
Like John and Paul, Dr. Castelli affirms that Framingham residents may be more knowledgeable about health risks than most other Americans, but they are no more likely to make major changes in their lifestyle until they feel personally vulnerable. Younger Americans tend to be more health conscious than their parents, he adds. Framingham offspring, for example, tend to have lower cholesterol levels than their parents did at the same age; their blood pressures also are lower and they smoke less.

Ronald, 42, a participant in the offspring study, reflects this trend. His father died of heart disease in 1967 at age 47. The odds were 50/50 that both Ron and his brother would inherit their father's predisposition to have excessively high cholesterol, but luckily, they did not.

"I quit smoking shortly after my father died and began exercising regularly; I now play squash three times a week," Ron reports. His wife, Linda, drastically altered the family diet. "We used to eat red meat virtually every night; now we rarely do. We eat chicken or fish, along with lots of salads, and we have fruit for dessert," she explains. Her recipes come from *The American Heart Association Cookbook*.

The couple does have one dietary indulgence: "We prefer the taste of butter to that of margarine," Ron admits. "But if my cholesterol level, now 155 mg/dl, were to go up, we'd cancel the butter," he claims.

"Diet is the key to wiping out the epidemic of heart disease in this country," Dr. Castelli asserts. "We know what to do, but we don't do it. We seem to be addicted to our lifestyle." Moreover, few physicians



"Diet is the key to wiping out the epidemic of heart disease in this country," Dr. Castelli asserts. ". . . Today I eat defensively. Fish, pasta, vegetables, fruits, and cereal grains are the staples of my diet."

Medical director Dr. William Castelli has applied Framingham findings to his own lifestyle. He jogs regularly.

seem interested in nutrition, he contends. "The main focus in American medicine is on the squeaky wheel, on treating acute crises; you have to be sick to get attention. Medical insurance will pay for coronary bypass surgery, but not for instruction on diets or other preventive care."

"For the first 10 years of the Framingham study, no one knew what the data meant," Dr. Castelli relates. "During the second 10 years, we had no proof that altering risk factors would make a difference. But during the third 10 years, the benefits of changing behavior became apparent."

"While doctors today are paying attention to high blood pressure, many still haven't picked up on cholesterol," he asserts. "They wait until total cholesterol is over 300 to take action. At that point, it's hard to budge. People whose cholesterol levels are under 250 are easier to change." The average cholesterol level of people in Framingham who get heart attacks is 244 mg/dl.

In a small study looking at the impact of diet on cholesterol levels, 21 strict vegetarians in Framingham were persuaded to eat meat for 4 weeks. By the end of that period, their total cholesterol rose by 19 percent. Their systolic blood pressure rose by 3 percent. Returning to the vegetarian diet reversed these effects. In vegetarians, whose total cholesterol levels tend to be lower than 150 mg/dl, heart attacks are rare, Dr. Castelli says.

The ratio of total cholesterol to HDL's (high density lipoproteins) is a better predictor of heart disease than the determination of total cholesterol alone, Dr. Castelli notes. "Anyone with a ratio of 4.5 or higher is in trouble," he asserts. Yet two-thirds of the men and half of the women in the United States are in this high-risk group.

Dr. Castelli, 53, is his own best advocate for a sensible lifestyle. He is from a high-risk family; both his father and brother had heart attacks in their forties.

"In 1977, just as we were becoming convinced that HDL's were important in protecting a person from a heart attack, my own total cholesterol was 270, and the ratio of my total cholesterol to my HDL's was 4.5," he relates. "I went on a prudent diet and started running; I had never previously exercised, and it took me 25 minutes to do 2 miles. Now, I'm down to about 16 minutes. My total cholesterol is 200, and my HDL ratio is much better, just over 3. Probably, I have modest disease because I got started too

late. Today, I eat defensively. Fish, pasta, vegetables, fruits, and cereal grains are the staples of my diet." And, he adds, "I never eat hamburgers, hot dogs, or salami."

What lies ahead for Framingham? Like Janus, the study simultaneously is looking toward aging and toward early predictors of heart and blood vessel disease.

As the Framingham population grew older, stroke became a natural focus of study. Dr. Philip Wolf, who heads this part of the Framingham study, comments, "Cerebrovascular accident, the term commonly used for stroke, implies whimsical bad luck. But stroke turns out to be the end of a chain of events set in motion many years before." The major underlying cause of stroke is high blood pressure, a fact previously suspected but first documented in Framingham, he adds.

"Today, the message that dramatic and marked elevation of blood pressure needs treatment is well accepted by both physicians and patients," says Dr. Wolf, who is a professor of neurology at Boston University. "But controversy still exists concerning the treatment of moderate and mild hypertension. Patients generally are asymptomatic; the damage proceeds silently. But once a person has had a stroke, the battle is essentially lost. Pulling out all the stops in the intensive care unit is too little, too late."

"Prevention," he insists, "is the answer." In fact, improved control of blood pressure has been associated with a more than 40 percent decline in U.S. stroke deaths in the last decade.

As Framingham offspring grow older, doctors hope to learn more about the role genetics plays in stroke. They also will look at the nature and degree of disability and the factors that determine whether someone who has had a stroke can be cared for at home or requires a nursing home.

The offspring joined the Framingham study in 1972. Eight years later, Joseph Stokes and his colleagues conducted followup exams that included exercise stress tests. "The abnormalities we saw on the exercise tests reflected the risk factor profiles made at the start of the study," reports Dr. Stokes, who is a professor of medicine at Boston University. "This finding highlights the usefulness of the exercise test, one of the few available noninvasive techniques for studying heart function, to predict coronary heart disease," he adds. Currently, the offspring study is exploring psychosocial issues with the aid of a lengthy self-administered questionnaire. Additionally, 24-hour food surveys will help show how the diet of the younger generation compares to that of their parents.

"The study is not supposed to alter participants' behavior," acknowledges Dr. Stokes, who worked full-time on the project in the 1950's and holds the distinction of being "examining physician number 10" on a roster that now numbers 78. "But if we see patients making mistakes in their health behavior, it's irresponsible not to counsel them," he insists.

Framingham, Dr. Stokes believes, has altered the way doctors practice preventive medicine. "It has provided a rational basis for assessing risks, identifying changes in health behavior to modify risk factors in helping the patient maintain good health."

"Framingham led the way and showed where intervention trials should go," he asserts. "It has done more than any other study in the history of mankind to identify the causes and consequences of coronary heart disease."

Judging the News

Breakthrough. Danger. Discovery. Heart attack-causing. Such words appear in newspapers, magazines, and books and on radio and television every day. Health and other scientific information comes to us not only as news, but also in the guise of entertainment, advertising, and even comic strips.

What sources can you trust? How can you judge whether you are getting conclusions based on solid evidence or merely opinions?

Most scientific information obtained by the general public is filtered through journalists who read scientific publications, attend conferences where scientists present their findings, and talk directly with the scientists themselves. Journalists and their editors also receive press releases from universities and medical centers, government agencies, drug companies, public relations firms, and even individual scientists. Thus, the media serve as "gatekeepers," and the issue of what gets reported and what does not is hotly debated within the field. Moreover, some scientists accuse journalists who write about science and technology of having an antiscience bias, while others claim they are guilty of indiscriminate, "gee-whiz" reporting.

What appears in the press or on the air may be a drastically condensed version of the story the reporter prepared, owing to the exigencies of available space or time. In addition, it is the nature of science to continually revise—what is true today may not be tomorrow.

So the burden is on the consumer who wishes to become better informed to ask questions. The following questions, adapted from those developed by the National Heart, Lung, and Blood Institute in conjunction with the Centers for Disease Control, are a good start:

- What are the scientists' qualifications? Are they speaking in their area of expertise?
- Do the scientists stand to gain financially from favorable reporting of their work?
- Was the research prospective (like the Framingham study, charting the natural history of the disease), retrospective (attempting to account for existing illness), or based on studies of people and animals or at a cellular level? Are the results based on observation or intervention?
- Have the findings been replicated by the same scientists and by others?
- How large was the study, and how widely can the results be applied?
- Are the findings part of an ongoing controversy? Do they support one side or another? Have conflicting points of view been presented?
- Would the results make you consider altering your personal health behavior—to use or to avoid a drug or vaccine, or to receive a type of x-ray or medical procedure? If so, do you have sufficient facts? If not, do you know where to go for more information?

Source of questions: *Using New Health Research*, Education Development Center, Inc., 1983 (funded by Division of Health Education of the Center for Health Promotion and Education, CDC, NHLBI, NIH, PHS, HHS contract #200-79-0922), p. 65.

Looking Ahead
Heart, Lung, and Blood Medicine in the Year 2000

Medicine is one field with no nostalgia for the good old days. Although medical history predates Hippocrates, the information base for modern medicine is less than 50 years old. Concepts we didn't understand and technologies that didn't exist as recently as 10 years ago are saving lives today. And scientists continue to learn new information at a geometric rate.

What does this knowledge explosion mean for the future of heart, lung, and blood medicine? Many things, and all of them good, say the experts.

First, according to specialists in heart, lung, and blood medicine, it means we have the tools and the knowledge in place for dynamic new medical care progress.

Knowledge and Tools for the Future

One of the keys to the future is the science of molecular biology. One of the discipline's most important tools for the future is recombinant DNA technology, sometimes called genetic engineering. Its significance for medicine is hard to overstate. In its two most dramatic applications, this technology can be used:

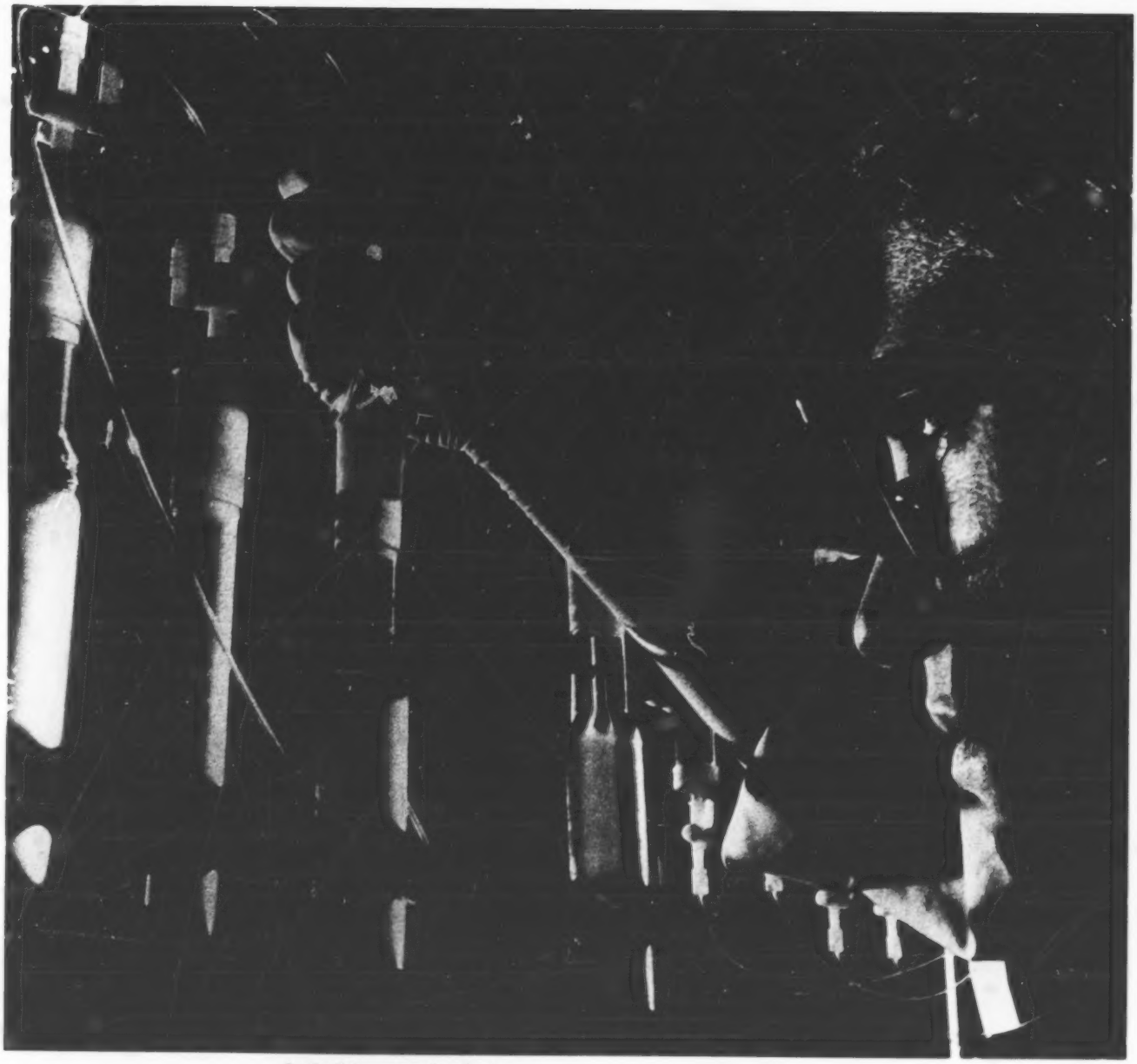
- To construct a radioactive "probe" that will locate a specific gene in human tissue. This gene can then be analyzed—for defects, as in a diagnostic test for genetic disorders, or simply to learn more about its structure and function.
- To produce and reproduce biological elements needed for medical therapy (as well as for agriculture or industry). These include drugs and therapeutic nondrug products such as proteins or clotting factors.

How does this technology work? A gene is essentially a specific sequence of elements (called nucleotides) in DNA that forms a code for the production of a substance, such as a protein. Each protein also has a specific sequence of amino acids that corresponds to the nucleotide sequence in the gene. By recognizing a protein sequence, scientists can reconstruct the corresponding gene sequence and actually "build" a chain of nucleotides that matches that of the target gene.

The building process is like a complicated gourmet recipe: There are many steps and a variety of exotic "ingredients." Enzymes called restriction endonucleases are used to cut DNA from human tissue into the desired pattern. The enzymes also cut DNA from yeast or bacterial cells (called the vector substance) into a complementary nucleotide pattern.

The human DNA is then added to vector DNA; the two bind together chemically and are mixed with another ingredient, usually the bacteria *Escherichia coli.* This combination produces copies, or clones, of the human-vector DNA fragment. The portion of the fragment containing the desired gene or sequence can then be isolated (using additional matched sets of nucleotide fragments) and "harvested," for use in gene probes, producing drugs and other therapeutic substances, or basic studies.

Another molecular biology tool with a Star Wars title is monoclonal antibody technology. This process fuses two cells into a hybrid cell with the properties of each parent. One parent cell is first immunized with an appropriate antigen. The hybrid can then be cloned to produce large quantities of pure antibodies specific to the antigen. These monoclonal antibodies have the ability to target even trace amounts of proteins from the blood. They thus have potential in pro-



A scientist uses small-scale chromatography to help purify a protein produced through recombinant DNA technology.

ducing proteins such as clotting factors that have therapeutic uses. The antibodies also have important diagnostic possibilities for congenital blood and thrombotic disorders. The textbooks say their potential long-term uses cannot even be imagined fully today.

A variety of other disciplines and technologies are also important tools for future progress. Cell biologists, for example, have recently developed the fastidious techniques necessary for cultivating the most critical human cell types. Analyzing these smallest living entities will allow an understanding of the basic mechanisms of life itself.

"This will be particularly important with regard to the heart," says Dr. Claude Lenfant, Director of the National Heart, Lung, and Blood Institute. "We now know a great deal about the heart's functions and its disorders, but considerably less about its most intimate mechanisms."

Epidemiology will provide statistical profiles of disease and risk with improved methods of data collection and analysis. New laser technology and more sophisticated imaging techniques will be important in diagnosis and treatment.

Where will these new tools lead? The experts offer a variety of predictions for probable advancements in treating and preventing disease.

Lung Disease

Halting Damage in Emphysema, Help for Transplants, Modifying the Immune Response

Dr. Lenfant calls the next 15 years the "age of intervention" for lung disease.

"Twenty years ago," he says, "science took a 'so-what' attitude about chronic lung disease, because very few people died from it and we could treat many of its symptoms. In the past decade, however, we began to focus more on basic mechanisms of the lung and its disorders. We now know it is possible to go beyond symptomatic relief to intervene in the disease process itself."

Emphysema is a good example of a condition for which this kind of intervention is likely to be widespread by the year 2000. We know from basic research that the normal lung has an exquisite balance between two chemicals, the proteases and the antiproteases. It also has a system of elastic fibers that lets the lungs expand and contract. When there is a protease-antiprotease imbalance, the lungs appear to lose the ability to protect themselves against chemical destruction of these elastic fibers. This is what happens in emphysema.

But, says Dr. Carl Franzblau, professor and chairman of biochemistry at Boston University School of Medicine, recent studies discovered two sources of the chemical imbalance: (1) a deficiency of a protein called alpha-1-antitrypsin (alpha$_1$ P$_1$) that protects the antiprotease system and (2) cigarette smoking. Some people with emphysema have a genetic defect that causes a deficiency of the protein shield alpha-1-antitrypsin. Cigarette smoking, which is the most common cause of chronic obstructive

The secretory mechanism of human lung mast cells (the concentric circles) is one subject of basic investigation in pulmonary medicine.

pulmonary diseases such as emphysema, also appears to disrupt the antiprotease inhibitors in people without an alpha$_1$ P_1 deficiency.

"Once we knew the cause," says Dr. Franzblau, "we developed approaches to replacing the missing alpha-1-antitrypsin. The techniques are still experimental, but the prospects for widespread application in the next 5 years are excellent. The gene sequence for alpha$_1$ P_1 has already been cloned, and industry has begun synthetic production of the protein using genetic engineering technology." It is probable, he adds, that replacement therapy will also be applied shortly to adult respiratory distress syndrome, which features the same protein deficiency. It may even have a long-term application to inhibiting atherosclerosis.

Thanks to the protective properties of a new drug, cyclosporin A, single lung transplants (rather than heart-lung transplants) may also become a viable option in the next 10 years. These transplants have been infrequently attempted in the past decade, and results were discouraging, largely because the patient's immune system frequently rejected the transplanted organ.

Dr. Frank J. Veith, chief of vascular surgery and director of the transplant program at Montefiore Hospital and Medical Center, says that cyclosporin A has the potential to change all that.

"Cyclosporin helps to suppress the immune response that rejects a transplant. It has markedly increased the success rate of single lung transplants in animal tests, and human transplants will be done experimentally in the near future if problems in procuring donor lungs can be solved. The drug has similar promise for heart-lung transplants, which better meet some patients' needs."

Dr. Alfred Fishman, William Maul Measey Professor of Medicine and director of the cardiovascular-pulmonary division of the University of Pennsylvania School of Medicine, believes that the inflammatory processes in lung disease are another exciting frontier.

The lung reacts to injury in different ways. Blood-borne cells are called to the site of injury to circumscribe the insult and to repair the damage. But once they arrive, they are orchestrated differently according to the nature of the injury. Some of the cells release substances that destroy lung tissue.

"In the next 10 years, we're going to be asking many questions about this process," Dr. Fishman notes. "What chemical message summons inflammatory cells to the site of injury? How can we separate the necessary action of these cells from the destructive? At what point in the process should we intervene? The answers to these questions are not far out of reach. The information will allow us to design an appropriate drug therapy for conditions such as chronic obstructive pulmonary disease."

Immunology may also hold the key to the fibrotic diseases such as cystic fibrosis. Unlike destructive lung disorders such as emphysema, which make the lungs baggy and less elastic, fibrotic conditions make the lungs too stiff. This occurs when the tissues overproduce materials such as collagen, a fibrous protein.

"We need to understand," says Dr. Franzblau, "what turns the cells on to make more of these substances than they need. Once we do, we will ask what materials we can add, in what well-defined way, to stop or temper overproduction. This is likely to occur by the turn of the century."

"Further down the line, perhaps by 2010,

molecular biology will probably allow us to turn off genes involved in overproduction or turn on genes that can help reverse the trend."

What other developments do the experts foresee in lung disease?

Unraveling the mechanism of disease in asthma and adult respiratory distress syndrome (ARDS) is likely to produce new therapies for these conditions. In asthma, studies in progress concern the nature of the airway obstruction and how to reverse it. In ARDS, recent research has explained how surfactant, the lining of the small airways that keeps the lungs expanded, disintegrates. Immediate work will focus on how to replace this important element therapeutically.

And Dr. Franzblau notes that the cigarettes made of vegetable leaves many people tried in their childhood may soon have an adult analogue. Scientists are now studying the composition of cigarette smoke, to isolate the specific elements with toxic effects. Theoretically, says Dr. Franzblau, this could lead to a reformulated cigarette with fewer or no harmful health effects.

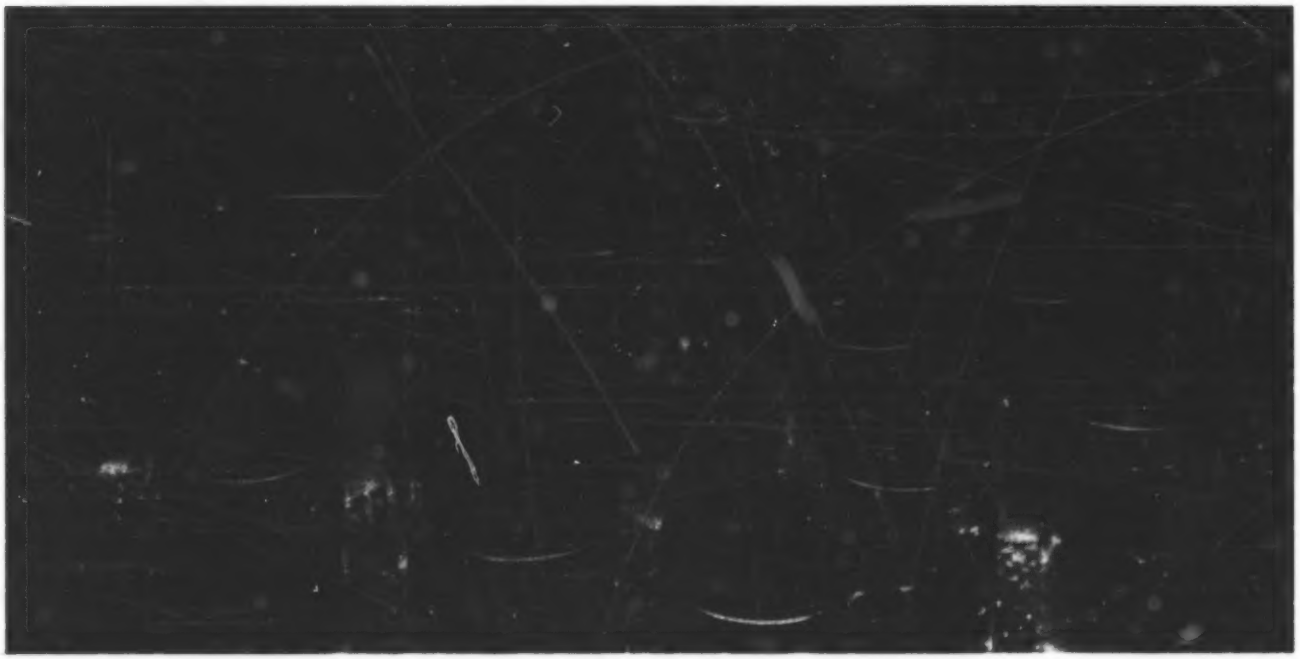
Heart Disease

New Treatments for Heart Attack, Lasers to "Clean" Arteries, a Totally Implantable Artificial Heart

Twenty years ago, the standard treatment for a heart attack patient was bed rest. With the advent of coronary care units, it became possible to monitor the patient's condition closely and control his heart rate, rhythm, and blood pressure through drugs. These interventions did not stop the heart attack, however, nor did they prevent the damage to the myocardium that occurs when heart muscle cells are deprived of oxygen.

In the next decade, this situation is likely to change. Medicine's ability to control the effects of or avoid heart attacks shows dramatic potential. New drugs and improving artificial devices point to a better outlook for patients with a variety of other heart problems as well.

The capacity to halt a heart attack before irreversible damage occurs lies in an experimental treatment called thrombolytic therapy. Physicians inject an enzyme either



Vials of freeze-dried tissue plasminogen activator await use in clinical tests of the enzyme in thrombolytic therapy.

through a vein or directly into the coronary artery to break down the blood clot in the coronary artery that causes an attack. Two enzymes, streptokinase and tissue type plasminogen activator, have been shown to restore blood flow to the heart, relieving chest pain and preserving healthy heart cells. Administered in the early stages of a heart attack, thrombolytic therapy could restrict the amount of lasting damage from a myocardial infarction.

A number of problems need to be resolved, however, before this therapy becomes routine, says Dr. Eugene Braunwald, of Harvard Medical School in Boston. Basic details of how much of which enzyme to use, when to inject it, and whether intravenous or direct injection into the coronary artery is more effective remain to be settled. But Dr. Braunwald believes that thrombolytic therapy could have a major impact on heart attack care—once controlled clinical trials answer questions definitively. It has potential as well in treating blood clots in other parts of the body.

Dr. John Ross, professor of medicine and head of the division of cardiology at the University of California, San Diego, School of Medicine, notes that other interventions for heart attack also hold promise for the future. Work is proceeding, for example, on drugs to protect the myocardium from damage until thrombolysis dissolves an occlusion. Better prognostic profiles using computers will allow physicians to recognize a need for bypass surgery or balloon angioplasty very early, perhaps before the recovering heart attack patient leaves the hospital.

In addition, better methods of limiting plaque growth through diet and drugs or removing plaque from the lining of the coronary arteries may avoid the progressive arterial narrowing that leads to heart attacks and stroke. Percutaneous transluminal coronary angioplasty (PTCA) is currently used for the latter purpose, usually when only a single vessel is impaired (see p. 32).

Dr. Michael Cowley, associate professor of medicine at the Medical College of Virginia, believes we do not yet know the boundaries of the technique's usefulness. "About 30,000 PTCA's were performed in 1983, and 50,000 to 75,000 are projected for 1984. As we have learned more about the technique and the technology itself has improved, some centers are beginning to perform PTCA experimentally in more severe cases: Two- or three-vessel involvement, total occlusions, and prior bypass patients, for example. While we have good data demonstrating short-term success, we need more long-term evidence before broader applications become routine."

A new technique using lasers to clear the vessels is also being tested. Lasers have already been used medically for photocoagulation in eye disease and to remove diseased tissue. By using a fiberoptic catheter to guide the laser beam, the physician should be able to visualize the impaired heart vessels and direct the beam to cut away plaque. This would offer another alternative to coronary bypass surgery for some patients.

The prospects are also improving for people with serious or end-stage heart disease. "In the next 15 years," Dr. Ross says, "we may be capable of inserting a totally implantable artificial heart. This improved heart will be smaller than the model we became familiar with in the experimental use in Dr. Barney Clark, with its large external power source. Machine designs are

Machine designs for artificial hearts are improving, and progress is also being made in resolving rejection problems in animal models.

A new technique using lasers to clear plaque from heart vessels is currently being tested. This image of a heart vessel partially occluded with plaque was produced during these experiments.

improving all the time, and progress also is being made in resolving technical problems using animal models.

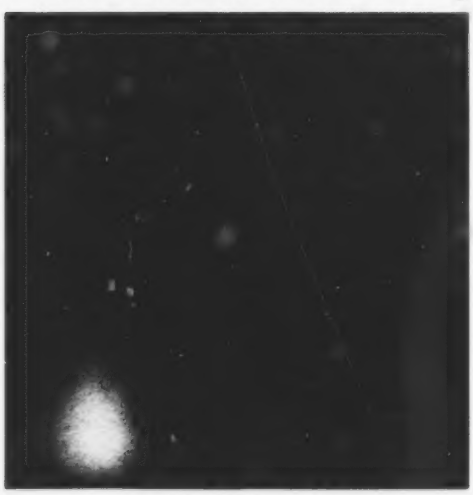
"With a larger donor program," adds Dr. Ross, "we could also see an increase in heart transplantation. The technology and the surgical techniques already exist."

The membrane called the endothelium may hold the key to improving another implantable device, the artificial heart valve. Dr. Alfred Fishman calls the endothelial layer in the blood vessels "the magic lining," because it interacts with each cell in the blood to maintain blood fluidity. The endothelium has a variety of other functions as well, but basic science is just beginning to unravel its biochemical actions.

When its mechanism is understood, explains Dr. Fishman, we should know why foreign substances such as an artificial device cause toxic effects in the blood. Better materials and techniques can then be developed to avoid rejection of a prosthesis.

Dr. Cowley believes that the prevention of sudden cardiac death will receive increasing attention in the next decade. "For some patients," he says, "death is the first manifestation of coronary disease. Improved diagnostic tools will help us identify potential victims, but it will never be feasible to screen everyone. We also need other kinds of markers to suggest which elements of the population are at high risk."

The future of heart medicine does not only encompass the new; it will also feature the improved. We already have drugs to prevent the erratic heart beats known as dysrhythmia. In the next 15 years, experts say we will have better drugs, with fewer side effects and easier regimens. We can already diagnose and monitor heart disease with an array of sophisticated equipment for visualizing internal processes (see p. 39). This equipment will get more sophisticated, allowing new applications and producing clearer, more accurate images.



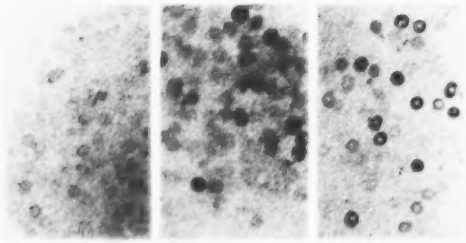
Hematologists have a head start: they can take blood from the body and study it, add or subtract elements to or from it, and put it back, with much greater ease than manipulating a solid organ or a tissue.

Blood Disease

Genetic Engineering to Fight Sickle Cell Disease and Hemophilia; New Therapies for Thalassemia

Techniques for diagnosing and treating blood disease are among the most advanced in medicine. But being a frontrunner is not surprising, says Dr. Jane Desforges, professor of medicine at Tufts University School of Medicine, because hematologists have a head start; they can take blood from the body and study it, add or subtract elements to it, and put it back, with much greater ease than manipulating an organ or a tissue.

The opportunity for indepth study of hemoglobin molecules has important implica-



Treatment with hydroxyurea "turns on" fetal globin genes in monkey red blood cells. In the first slide, there is no fetal hemoglobin (the dark circles) in the cells. At day 82, 6 days after a course of treatment with hydroxyurea, fetal hemoglobin appears (slide 2). Slide 3 shows a substantial amount of fetal hemoglobin, following six courses of hydroxyurea treatment.

tions for the future. The most dramatic is the potential ability to "turn on" a gene that could correct anemia in sickle cell disease. We know, Dr. Desforges says, that the body makes one kind of hemoglobin for a fetus *in utero* and another kind for children and adults, each with a different genetic makeup.

Adult hemoglobin contains subunits of beta globin genes, mutations of which cause sickle cell disease and other genetic disorders. Fetal hemoglobin does not. Researchers already knew that adults can use fetal hemoglobin without adverse effects. They thus reasoned that turning on the fetal hemoglobin gene could be therapeutically valuable.

Initial attempts to manipulate these genes involved a cancer drug called 5-azacytidine. Studies in baboons showed that this drug stimulates fetal hemoglobin synthesis; experimental use in sickle cell patients increased production of fetal hemoglobin and correspondingly decreased sickled hemoglobin. Researchers still don't understand how 5-azacytidine works, however, and its use clinically is complicated by very toxic effects at high doses.

While scientists continue to explore the mechanism of gene turn-on, they are also experimenting with other drugs. Hydroxyurea is currently under investigation and appears to have the effects of 5-azacytidine with fewer complications.

"We are close enough to understanding this process," says Dr. Desforges, "that clinical applications are very likely by the year 2000."

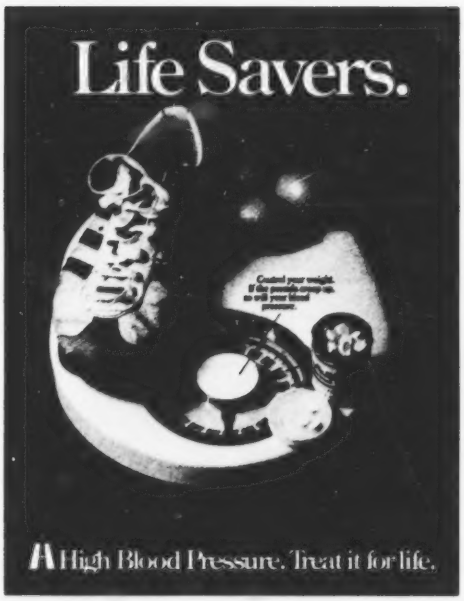
Molecular biology is also on the threshold of a major breakthrough for patients with hemophilia and other hereditary clotting and bleeding disorders. Using monoclonal antibody and recombinant DNA techniques, genes have been cloned for most of the clotting factors and a number of related proteins, called fibrinolytic enzymes.

These studies make it possible, says Dr. Harold Roberts, professor of medicine and pathology, and chief of the division of hematology at the University of North Carolina School of Medicine, to study the regulation of these substances. We can then answer such questions as what biological signals begin and shut down their production. It should also be possible to produce synthetic clotting factors and fibrinolytic enzymes using cloning techniques. Drug companies have already begun preliminary studies that may lead to the synthetic production process for the clotting factor used in hemophilia therapy, factor VIII. Factor VIII is currently produced for therapy by extracting it from donated blood. Artificially produced factor VIII will have a significant advantage, however; it will be a pure product, free of the danger donor blood presents of contamination by AIDS or hepatitis viruses.

"According to the Hemophilia Council," says Dr. Roberts, "synthetic production of the other clotting factors should be feasible within the next 5 years. We should have animal models of hemophilia A and hemophilia B that can be used to study genetic aspects of coagulation disorders."

Dr. Desforges also believes another kind of genetic therapy may become a reality in the more distant future: Inserting a normal gene into the bone marrow of a patient with a hereditary disorder such as thalassemia. It is feasible to remove the marrow, treat it, and then reinfuse it. Globin genes have already been cloned and techniques described for their insertion. Experiments are still needed, however, to determine whether

Prevention of illness will be an important focus in the next 15 years, particularly for cardiovascular disease.



the inserted normal gene would produce enough normal hemoglobin to be therapeutic, without associated effects. The prospects are particularly bright for thalassemia, in which there is a profound deficiency of certain globin chains, but no abnormal globins present.

Thalassemia patients also have another, shorter term option. The techniques have been developed for transplanting healthy bone marrow from a matched donor, and this procedure has been used to treat several life-threatening blood diseases. "Children with severe thalassemia have little hope of leading a normal life," Dr. Desforges notes. "For those with an appropriate donor, even the risks associated with transplantation may become acceptable."

As is the case with heart and lung disease, the future holds better diagnostic tools and drug therapy for blood diseases. Dr. Roberts says that magnetic resonance scanning will allow physicians to visualize thrombi, or blood clots, in the veins and arteries, and beta ultrasound will allow them to pinpoint sclerotic lesions in the vessels.

Dr. Desforges points to current trials of new drugs for sickle cell disease that inhibit the sickling process and relieve symptoms during a crisis. Another new agent, desferol, promises major benefits for patients who need transfusions for long periods of time. This drug prevents the iron overdose that often accompanies long-term transfusion requirements. Already in experimental use for thalassemia, desferol should also prove useful for patients with aplastic anemia and other states in which red cell production is ineffective.

Beyond Treatment

Disease Prevention

Health advances in the 20th century have come as often from preventing disease as from improving treatment. Prevention is usually more difficult, however, because it requires understanding the fundamental causes and mechanisms of a disease.

This will be an important focus in the next 15 years, particularly for cardiovascular disease. The experts say we are likely to learn much more about risk factors for heart disease and stroke and how to reduce them. Critical concerns include:

- The idea of susceptibility. Why, for example, are some people who eat high sodium diets prone to develop high blood pressure, when others can eat all the salt they want without harm? When we understand this mechanism, we will be able to pinpoint those who should avoid salt.
- Predicting occurrence and outcome of disease. The concept of "risk factors" for disease has been firmly established. Groups of people can be classified according to level of risk, but we cannot yet

predict which individuals will develop a disease. Studies are under way to increase the sensitivity of current risk profiles. The overall effects of having different combinations of risk factors and differences in risk in different geographic areas or age groups will become better understood.

- Helping people modify unhealthy behaviors. Telling a person that smoking, overeating, or other behaviors are bad clearly is not enough to make him or her change unhealthy habits. One of the most critical areas of research is exploring what motivates people to change their behavior, what skills they need to do it, and how they can maintain new habits for a lifetime. Topics we should learn a great deal more about in the next 10 years include: Which smoking cessation techniques are most effective; what are the most effective diets and approaches to reducing sodium and cholesterol; and how does health professional-patient communication affect behavior change.
- Identifying the causes of heart disease. Dr. Claude Lenfant believes that in the next 20 years scientists will elucidate the key to preventing cardiovascular disease: understanding its causes. We still do not know, for example, what combination of factors leads to high blood pressure, heart attack, or stroke. Understanding the most intimate mechanisms of the heart is principally a task for basic scientists. With this understanding, we can develop new approaches to prevention. One example is the possible relationship of diet to blood clotting. Once platelet aggregation responses become clear, we may be able to modify our diets to avoid a clotting response that leads to heart attack or stroke.

Following All the Paths to Progress

The experts disagree about whether the next 15 years will see a similar—or greater—level of medical progress than the past 15. Dr. Lenfant believes that the difference may be less in the amount of progress than in the kind of advancements that occur. "We are unlikely," he says, "to see the same kind of quantitative progress that has marked the past 10 years. We have already reduced coronary heart disease mortality by 25 percent and stroke mortality by 40 percent. We won't see another 25 or 40 percent reduction by the year 2000, because there is a limit to how far you can push back the time of death.

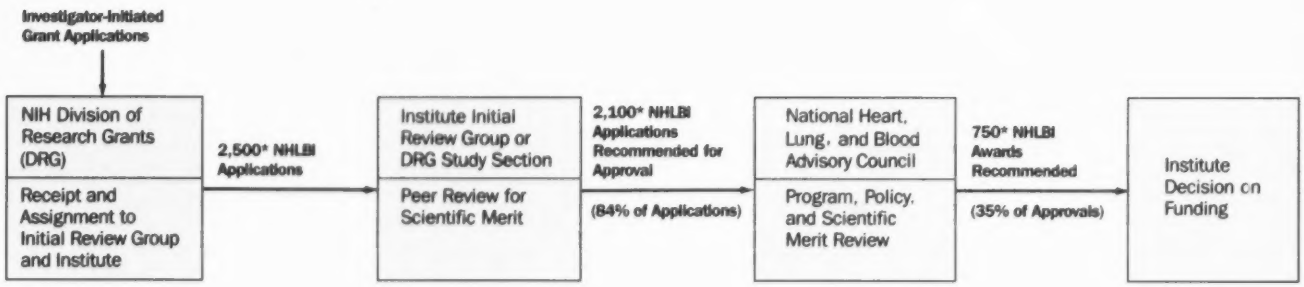
"What we will see are advances that are qualitatively more important, because we will be going deeper and addressing the most serious questions medicine has to ask. These advances will enhance the quality of health during our longer lifespan."

Dr. Lenfant also believes that only a multifactorial approach will produce the breakthroughs we've come to expect of modern medicine.

"We need to move into the future from both ends of the biomedical research continuum. We need to have a focus on basic science and clinical applications. But we have to balance it by validating and demonstrating new approaches and research in prevention. With a comprehensive approach, there is every reason for optimism."

Research
How Is It Supported?

Peer Review and Award Process for Grants

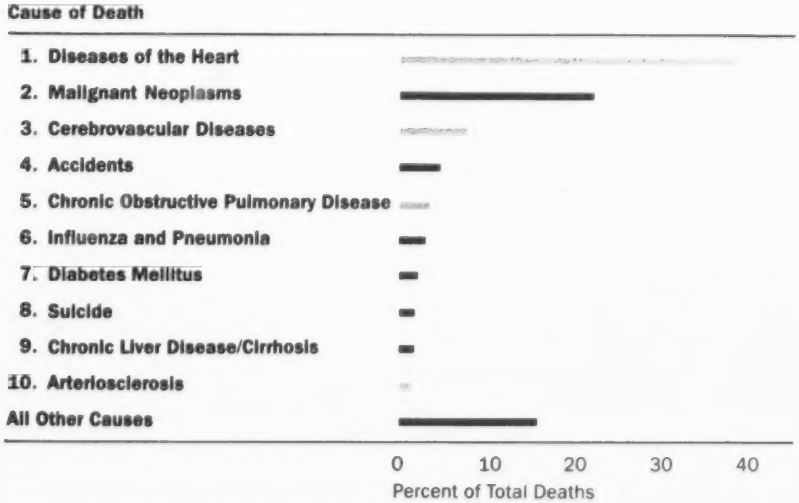

Investigator-Initiated Grant Applications
NIH Division of Research Grants (DRG)
Receipt and Assignment to Initial Review Group and Institute
2,500* NHLBI Applications
Institute Initial Review Group or DRG Study Section
Peer Review for Scientific Merit
2,100* NHLBI Applications Recommended for Approval
(84% of Applications)
National Heart, Lung, and Blood Advisory Council
Program, Policy, and Scientific Merit Review
750* NHLBI Awards Recommended
(35% of Approvals)
Institute Decision on Funding

*Numbers are approximate

Heart, Lung, and Blood Disease
Health and Economic Consequences

Table 1

10 Leading Causes of Death in the United States



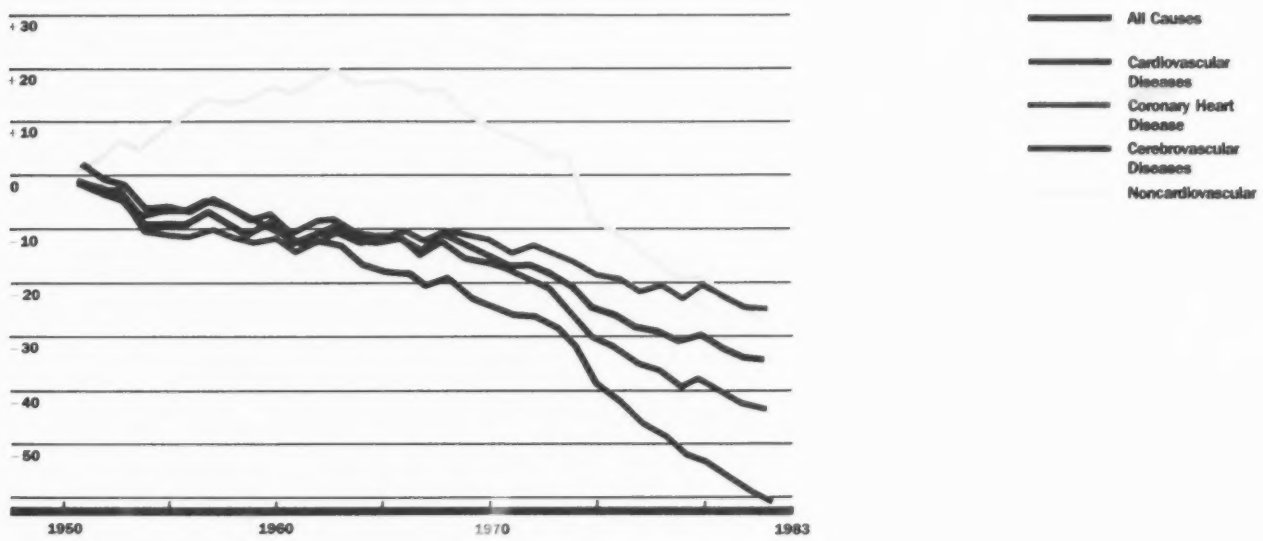
Shaded bars indicate heart, blood vessel, lung, and blood diseases.
Figures are for 1982.

In 1983, about 2 million Americans died. More than half of those deaths were attributable to four causes: diseases of the heart, cerebrovascular diseases, chronic obstructive pulmonary disease, and arteriosclerosis.

80

Table 2

The Good News: Trends in Mortality for Cardiovascular Diseases



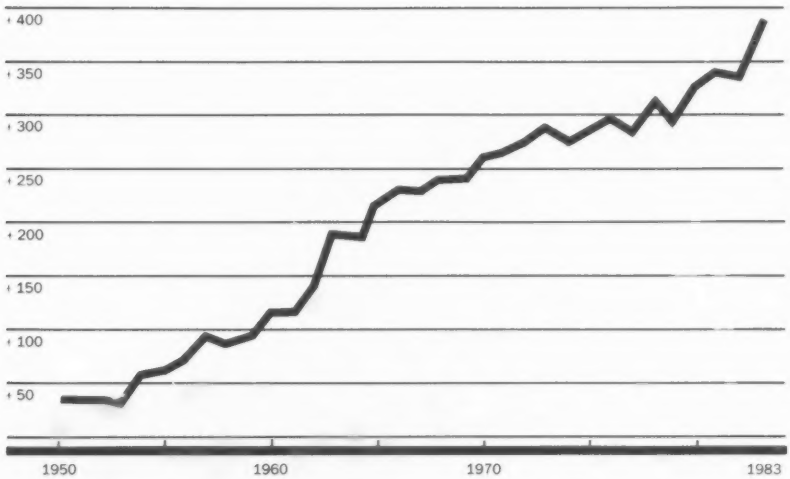
Americans are enjoying better health than ever before. During the past several decades, the overall death rate has declined and life expectancy has increased for all segments of the population.

Leading the trend has been the decline in deaths attributable to cardiovascular disease. Over the past 20 years, the age-adjusted death rate for all cardiovascular diseases dropped by 38 percent, in comparison with a decrease of 16 percent in noncardiovascular deaths. This reduction in cardiovascular mortality rates accounted for 72 percent of the overall national mortality reduction and for the major portion of the increase in life expectancy during that period.

Coronary heart disease has been a great concern as the major cause of death in men over 40 and in women over 50. While overall death rates declined, coronary deaths increased up through the 1960's, reaching a peak in 1963. Since that time, mortality has decreased dramatically; the decline coincides with better management of patients with risk factors, improved treatment of acute episodes, and greater efforts at secondary prevention.

Table 3

The Bad News: Death Rates for Chronic Obstructive Pulmonary Disease



Age-adjusted death rates for COPD* expressed as percent change from 1950 rate

*Includes asthma

Ten million Americans are afflicted with chronic obstructive pulmonary disease (COPD), which embraces emphysema and chronic bronchitis.

While deaths from other causes have been declining, deaths attributable to COPD have increased sharply in recent years, especially among women.

This phenomenon parallels the trend seen in lung cancer and is closely tied to patterns of cigarette smoking.

Table 4

The Cost of Heart, Lung, and Blood Diseases

Heart

- 60 million Americans (26% of the population) suffer from heart disease or hypertension.
- 1 in 3 males and 1 in 10 females can be expected to develop some major cardiovascular disease *before age 60*.
- Hypertension, the most prevalent cardiovascular disease, affects 46% of Americans in the 45–65 age group and 66% of those over age 65.
- Each year, cardiovascular diseases account for:
  875 million days of restricted activity
  264 million bed days
  26 million lost work days.
- The cost of cardiovascular diseases is the largest for any diagnostic group. In 1982, these diseases accounted for:
  $41.2 billion in direct costs—1% of the GNP
  $52.6 billion in indirect costs (from loss of productivity and premature death).
- Coronary heart disease is the leading cause of premature disability in the U.S. labor force and accounts for 19% of the disability allowances paid by the Social Security Administration.

Lung

- In the United States, approximately one person in five has a chronic respiratory problem.
- 10 million Americans suffer from chronic obstructive pulmonary diseases; 7.2 million have asthma.
- Respiratory diseases rank first as a cause of both doctor's visits and bed disability days.
- Each year, lung diseases account for:
  22 million physician visits
  21 million days of hospital care
  2.7 million hospital discharges.
- In 1981, the tab for lung diseases was:
  $7.6 billion in direct costs
  $18.8 billion in indirect costs.

Blood

- Blood-related disorders affect millions of Americans, both as primary diseases and as contributors to such diverse conditions as stroke, myocardial infarction, diabetes, hypertension, cancer, liver disease, and nephritis.
- In 1978, blood diseases were reported on death certificates as the underlying cause of 351,322 deaths and as contributing factors in 579,846 deaths.
- Sickle cell anemia afflicts nearly 50,000 black Americans; two-thirds of them can expect to die by age 35.
- Over 20,000 Americans have hemophilia. While the disease causes few deaths, the majority of its victims require lifetime treatment with antihemophilic factor at an average annual cost of $4,000 per patient.
- In 1983, blood diseases accounted for:
  1.7 million hospitalizations
  17.6 million hospital days
  6.8 million office visits
- The cost of blood diseases in 1982 was:
  $1.5 billion in direct costs
  $700 million in indirect costs.

Acknowledgments

Managing Editor
Joy Roff Mara

Contributing Authors

1. From Theory to Practice: The Biomedical Research Spectrum—Joy Roff Mara
2. Pathways to Discovery—Dodi Schultz
3. Function and Failure: Visualizing Heart, Lung, and Blood Disease—Estelle Schwalb
4. The Era of Technology—Lawrence Galton
5. Life Savers: Advances in Medical Treatment—William A. Check, Ph.D.
6. Improving the Outlook for Children—Dodi Schultz
7. Prevention: Framingham's Legacy—Lynne Lamberg
8. Looking Ahead: Heart, Lung, and Blood Medicine in the Year 2000—Joy Roff Mara
9. Heart, Lung, and Blood Disease: Health and Economic Consequences—Barbara Marzetta Liu

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